A MULTIMETHOD, PATIENT-ORIENTED EXAMINATION OF PAIN IN CHILDHOOD CANCER SURVIVORS

by

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Dalhousie University is located in Mi'kma'ki,
the ancestral and unceded territory of the Mi'kmaq.
We are all Treaty people.

To my parents, Julie and Avi,

Who from a young age, nurtured my dreams, and instilled in me the value of education.

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ABSTRACT

Emerging theory and empirical work suggest that pain is a significant late effect of childhood cancer and trigger of fear of cancer recurrence (FCR). This dissertation aimed to: explore the experience and meaning of pain after childhood cancer (Study 1); experimentally quantify differences in pain and sensory functioning in childhood cancer survivors (Study 2); adapt and validate self-report measures of FCR for childhood cancer survivors and parents (Study 3); and examine the relationships between pain, anxiety, pain catastrophizing and FCR in childhood cancer survivors and their parents (Study 4). Study 1 presents the findings from a qualitative study that explored the experience and meaning of pain in 10 childhood cancer survivors (ages 8-18 years) and their parents. Three superordinate themes were generated: (a) pain is a changed experience after cancer; (b) pain may be interpreted as a threat; and (c) pain interpretation occurs within the context of how the cancer experience is appraised. In Study 2, 56 childhood cancer survivors (ages 8-17 years) completed a standardized quantitative sensory testing (QST) protocol. Results revealed pervasive sensory differences compared to reference values present years after treatment completion. Demographic, clinical, and psychosocial risk factors for differences in sensory processing were identified. In Study 3, the Fear of Cancer Recurrence Inventory (FCRI) was adapted for childhood cancer survivors (the FCRI-Child) and parents (the FCRI-Parent). Psychometric properties of the adapted measures were examined. Data were collected from 124 survivors (ages 8-18 years) and 106 parents. The FCRI-Child and FCRI-Parent demonstrated strong internal consistency, construct validity, and criterion validity. Study 4 summarizes the relationship between anxiety, pain intensity, pain catastrophizing, and FCR in the sample of childhood cancer survivors and parents from Study 2. For survivors, greater anxiety symptoms were associated with increased pain intensity, pain catastrophizing, and FCR. For parents, greater anxiety symptoms and pain catastrophizing, but not child pain intensity, were associated with FCR. Pain catastrophizing predicted unique variance in parent and child FCR. Taken together, this dissertation contributes to the understanding of pain after childhood cancer and its relationship with FCR. Findings point to potential targets for intervention for this complex population.

LIST OF ABBREVIATIONS AND SYMBOLS USED

°C	Degrees Celsius
Δ	Change
ALL	Acute Lymphoblastic Leukemia
BVS-C	Body Vigilance Scale – Child
CCS	Childhood Cancer Survivor
CDT	Cool Detection Threshold
CI	Confidence Interval
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CNS	Central Nervous System
CPT	Cold Pain Threshold
CTI	Cancer Threat Interpretation
d	Cohen's *d*
DFNS	German Research Network on Neuropathic Pain
DMA	Dynamic Mechanical Allodynia
EFA	Exploratory Factor Analysis
FCR	Fear of Cancer Recurrence
FCRI	Fear of Cancer Recurrence Inventory
FCRI-C	Fear of Cancer Recurrence Inventory – Child
FCRI-P	Fear of Cancer Recurrence Inventory – Parent
FCRI-SF	Fear of Cancer Recurrence Inventory – Short Form
HADS-A	Hospital Anxiety and Depression Scale - Anxiety Subscale
HPT	Heat Pain Threshold
IPA	Interpretive Phenomenological Analysis
IQR	Interquartile Range
ITR-3	Intensity of Treatment Rating Scale 3.0
IUS-12	Intolerance of Uncertainty Scale – 12 items
IUS-C	Intolerance of Uncertainty Scale – Child
M	Mean
MCAR	Missing Completely at Random
MDT	Mechanical Detection Threshold
MPS	Mechanical Pain Sensitivity
MPT	Mechanical Pain Threshold
N	Population Sample Size
n	Sub-sample Size
mN	Millinewtons
NRS	Numerical Rating Scale
p	P-value for Testing Significance
PCS-C	Pain Catastrophizing Scale for Children

PCS-P	Pain Catastrophizing Scale for Parents
Ped-mTNS	pediatric-modified Total Neuropathy Score
PNS	Peripheral Nervous System
QST	Quantitative Sensory Testing
r	Pearson's Correlation Coefficient
R^2	Proportion of variance explained in regression analyses
RCADS-25	Revised Children's Anxiety and Depression Scale short version
SCT	Stem Cell Transplant
SD	Standard Deviation
ß	Standardized Regression Coefficient
t	Value for t-test
WDT	Warm Detection Threshold
WUR	Wind-Up Ratio
α	Cronbach's Alpha
τb	Kendall's Tau-b

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CHAPTER 1: INTRODUCTION

1.1. Pain and Childhood Cancer

Each year, approximately 1,000 Canadian children and adolescents between the ages of 0-14 years are diagnosed with cancer (Canadian Cancer Statistics Advisory Committee, 2019). Leukemia (35%), central nervous system cancers (18%), lymphoma (13%), neuroblastoma (7%), and soft tissue sarcoma (7%) are the most common diagnoses in this age group (Canadian Cancer Statistics Advisory Committee, 2019). Improvements in survival rates and the development of increasingly aggressive treatment protocols have highlighted the importance of optimizing supportive care for children with cancer. Retrospective reviews of symptom patterns at diagnosis have identified pain as one of the most common presenting symptoms for children with cancer (Jonsson et al., 1990; Miser et al., 1987; Reulecke et al., 2008). Unfortunately, pain often continues over the course of a child's treatment and beyond. Estimates suggest that 45-86% of children with cancer experience pain, often prolonged, across the disease trajectory (Twycross et al., 2015). Pain is among the most common and distressing symptoms reported by children with cancer and their parents (Collins et al., 2000; Hedström et al., 2003; Jacob et al., 2008; Miller et al., 2011; Van Cleve et al., 2012). Cancer-related pain is a complex phenomenon and its causes can be diverse. For children with cancer, pain can result from medical treatments (e.g., chemotherapy, immunotherapy, radiation therapy), skin-breaking procedures (e.g., port accesses, lumbar punctures), and the disease itself (e.g., tumour-related nerve compression) (Twycross et al., 2015). Not only is cancer pain common for children, but it can also be interfering. Children with cancer have rated pain as one of the top two most bothersome symptoms (Miller et al., 2011) and have described

pain as the most anxiety-provoking aspect of hospitalization (Jacob et al., 2008). When untreated, cancer-related pain can have serious short- and long-term consequences, including decreased quality of life (Calissendorff-Selder & Ljungman, 2006; Eiser et al., 2005), poor sleep (Walter et al., 2015), social, emotional and behavioural problems (Ameringer, 2010; Steif & Heiligenstein, 1989), and increased distress (Katz et al., 1980) and pain sensitivity (Weisman et al., 1998) during future procedures.

1.2. Childhood Cancer Survivorship

Survival rates for children diagnosed with cancer have improved substantially over the past five decades. Approximately 84% of children with cancer across all diagnoses are now expected to become long-term survivors, reflecting a 50% increase from the 1970s (Siegel et al., 2016). In 2020, there were an estimated 500,000 childhood cancer survivors living in North America alone (Robison & Hudson, 2014). As survival rates have increased, so has an appreciation for the physical and psychological challenges faced by childhood cancer survivors and their families. A discussion of cancer survivorship would be remiss without acknowledging the debate around the term 'cancer survivor' (Marzorati et al., 2017). In this dissertation, the term 'survivor' is used to describe individuals who have completed treatment with curative intent and are cancer free. It is important to note, however, that not all people with a history of cancer identify with this term and definition (Cheung & Delfabbro, 2016).

Much of what is known about the late effects of childhood cancer has been through large cohort studies of adult survivors of childhood cancer (Hudson et al., 2011; Robison et al., 2002). In one of the only population-level studies examining the burden of morbidity faced by childhood cancer survivors still in childhood, Phillips and colleagues

(2015) found that two-thirds of survivors between the ages of 5-19 years had a chronic health condition, and one-third of all childhood cancer survivors suffered from a condition that was severe or life-threatening (S. M. Phillips et al., 2015). The most common late physical effects of childhood cancer include pulmonary, auditory, endocrine-reproductive, and neurocognitive impairments (Hudson et al., 2013), which can result in lower health-related quality of life (Yeh et al., 2016), greater functional limitations (Dowling et al., 2010), and increased risk for frailty (Hayek et al., 2020). Secondary malignancies can also develop (Turcotte et al., 2017) and some childhood cancer survivors remain at lifelong risk that their primary cancer could recur (Wasilewski-Masker et al., 2009). While many survivors of childhood cancer now live well into adulthood (Siegel et al., 2016), the above-mentioned late effects of treatment place survivors at significantly greater risk for early mortality compared to individuals without a history of childhood cancer (Yeh et al., 2020).

In addition to late physical effects of treatment, survivors of childhood cancer are at risk for psychological sequalae (Michel et al., 2020); however, research in this area has yielded conflicting findings. A recent review on psychological outcomes in adolescent survivors of childhood cancer found that across studies, only 10-20% of survivors reported psychological problems (Mertens & Marchak, 2015), which is largely in line with estimates in the general population (Kessler et al., 2007; Whitney & Peterson, 2019). While many survivors of childhood cancer demonstrate psychological resilience, a significant number also describe challenges following the completion of treatment (Wakefield et al., 2010) such as decreased positive mood and lower self-esteem (Von Essen et al., 2000), negative body image perceptions (Pendley et al., 1997), symptoms of

post-traumatic-stress (Kazak et al., 1999) and worries about the future (e.g., recurrence, fertility) (Marchak et al., 2015; Weigers et al., 1998). Studies using clinical cutoff scores likely underestimate the psychological challenges experienced by survivors of childhood cancer. Generic measures of psychological functioning may not adequately capture the specific psychological difficulties that survivors experience (McDonnell et al., 2017), which may still be impairing and require intervention (Michel et al., 2020).

1.3. Pain as a Late Effect of Childhood Cancer

Despite the central role that pain plays in the diagnosis and treatment of childhood cancer, pain in the survivorship period has received relatively little attention. An emerging body of literature has pointed to pain as a significant late effect for cancer survivors. Long-term follow-up studies on the physical health of adult cancer survivors suggests that pain persists for 30-60% of survivors, even years after the expected healing period following the completion of treatment (Brown et al., 2014; Glare et al., 2014; Harrington et al., 2010; van den Beuken-van Everdingen et al., 2007). This is in contrast to the estimated 20% of adults in the general population (Dahlhamer et al., 2018) that experience chronic pain. Harrington et al. (2010) systematically reviewed the literature on the symptom burden experienced by adult breast, gynecological, prostate, and colorectal survivors and found that pain was one of the most common symptoms experienced by survivors. Pain may be the primary concern or secondary to other chronic conditions that are late effects of treatment (Glare et al., 2014).

Research on pain in survivors of childhood cancer is sparse but the studies that have been conducted have found that pain may be also prevalent and clinically significant in this population. The reported prevalence of pain after treatment for childhood cancer is

broad, ranging from 4.3-75% (Alberts et al., 2018; Reinfjell & Zeltzer, 2020; Schulte et al., 2021), likely because of the use of non-validated and single item pain assessment tools across studies. Thus, while approximately 20% of children in the general population are estimated to experience chronic pain (King et al., 2011), it is unclear how the proportion of childhood cancer survivors compares. There is also limited information on risk factors for pain after childhood cancer. Research has consistently found links between female sex and fatigue and increased risk for pain (Schulte et al., 2021), though the directionality of the relationship between pain and fatigue remains unclear. Evidence for other determinants has been weak, though preliminary findings suggest that factors such as younger age at diagnosis, older age at assessment, and history of certain diagnoses (e.g., central nervous system tumors, bone tumors, soft tissues sarcomas, retinoblastoma, and high risk acute lymphoblastic leukemia) may be associated with pain (Reinfjell & Zeltzer, 2020). Pain has been associated with numerous adverse outcomes for survivors of childhood cancer, such as emotional distress, and decreased quality of life (Alberts et al., 2018; Reinfjell & Zeltzer, 2020; Schulte et al., 2021). Similar to the literature on other late effects, much of the research on pain has been conducted in adult survivors of childhood cancer (Alberts et al., 2018; Reinfjell & Zeltzer, 2020; Schulte et al., 2021). The field has also been limited by its reliance on non-validated screening questionnaires that are often based on retrospective recall.

Reasons for persistent pain in survivors of childhood cancer are unclear; however, the neurological impacts of cancer and its treatment likely play a role. Childhood cancers can cause direct damage to the nervous system and its treatments can contribute to further nerve injury (N. S. Phillips et al., 2021). Many childhood cancers require prolonged or

intense exposure to neurotoxic chemotherapeutic drugs (e.g., vinca alkaloids, platinums, glucocorticosteroids), which can cause dysfunction of the small- and large- nerve fibres and neuropathy (Zajączkowska et al., 2019). Chemotherapy-induced peripheral neuropathy (CIPN) is among the most well-studied neurological sequelae of childhood cancer. It is estimated that while upwards of 87% of children experience CIPN during active treatment (Gilchrist et al., 2017), 30-50% continue to show deficits when followed-up months to years later (Gilchrist et al., 2017; Kandula et al., 2018). Over the course of treatment, children may also experience nerve injury from radiotherapy (Balentova & Adamkov, 2015). Repeated skin-breaking procedures (e.g., venipunctures, port accesses, lumbar punctures), and major surgery, are also common in cancer treatment and can lead to upregulation of nociceptive function and prolonged pain (Bisogni et al., 2014; Voscopoulos & Lema, 2010).

Acute nociceptive damage, such as that caused by cancer and its treatment, may induce long-term changes that prime the sensory processing pathways to become upregulated during subsequent pain (La Hausse de Lalouviére et al., 2014). This may be especially true for survivors of childhood cancer, as insults to the nervous system in childhood - a time of somatosensory maturation and development - can result in lasting changes to pain processing (Andrews et al., 2002; Walker et al., 2009). However, with advancements in pain science, it has become clear that the variance observed in pain processing cannot be explained by biological factors alone. Psychosocial factors modulate the cognitive and affective aspects of somatosensory functioning and play a central role in the experience of pain (Eccleston & Crombez, 1999; Melzack & Wall, 1965; Ryckeghem et al., 2019).

1.4. Psychosocial Factors and Pain

Contemporary pain theories highlight the importance of psychosocial factors in the experience of pain (Eccleston & Crombez, 1999; Melzack & Wall, 1965). A robust body of literature supports this notion with evidence suggesting that an individual's experiences of pain can be altered by factors such as levels of anxiety and depression (Woo, 2010), degree of pain catastrophizing (Vervoort et al., 2006), past pain experiences (Weisman et al., 1998), memories of pain (Chen et al., 2000), and how threatening pain is perceived to be (Boerner et al., 2016). Given the nature of the disease and its treatment, cancer-related pain is often experienced in the context of difficult thoughts and feelings. For children who have had cancer, pain may have been associated with distress (Penner et al., 2008), uncertainty (Fortier et al., 2013), and thoughts about death and dying (McCaffrey, 2006). According to cognitive-affective theories of pain (Eccleston & Crombez, 1999; Ryckeghem et al., 2019), these psychosocial factors would play an important role in how childhood cancer survivors experience and interpret pain. However, almost no research exists regarding how having cancer shapes children's experience of pain, or the meaning they attribute to these experiences, during the survivorship period.

Pain is not experienced in isolation, but rather, within the broader social and ecological systems in which it occurs (Craig, 2009). For children, the family is a fundamental social context in which they experience pain. There is strong evidence to suggest that parental distress (e.g., anxiety, catastrophizing about their child's pain) is linked with worse child outcomes, such as increased pain, internalizing symptoms, and functional disability (Caes, Goubert, et al., 2014; Chow et al., 2016). The ways in which

parents *respond* to their child's pain have an important role in the relationship between parent distress and child outcomes in experimental (Moon et al., 2011), procedural (Campbell et al., 2017), and chronic pain (Palermo & Chambers, 2005) contexts. For instance, in children with chronic pain, parents who catastrophize more about their child's pain engage in more protective (e.g., reinforcement of and attention to pain) and avoidant behaviors, which in turn, increase child pain and functional disability (Sieberg et al., 2011; Simons et al., 2015). Similar relationships have been found in the context of pediatric acute pain (R. W. Smith et al., 2007), including in cancer-related painful procedures (Caes, Vervoort, et al., 2014; Dahlquist et al., 1995; Dahlquist & Pendley, 2005; Rheel et al., 2021).

In the cancer survivorship literature, family caregivers' worry and distress about a survivor's health has been found to significantly impact survivors' worry and distress (Mellon et al., 2007). While parents of childhood cancer survivors report concerns about their child's health and future (Fletcher, 2010; Leventhal-Belfer et al., 1993; Wakefield et al., 2011), the impact that this distress has on children's pain-related and other outcomes in survivorship is unclear. Based on what is known about the relationship between parent and child outcomes in pediatric pain (Higgins et al., 2021), parental factors may be important predictors of children's pain and psychosocial functioning in survivorship. This dissertation builds on previous work in the pediatric pain literature by considering the parental social context in children's experience of pain after childhood cancer.

1.5. Fear of Cancer Recurrence

A pertinent psychosocial factor unique to the cancer survivorship context is fear of cancer recurrence (FCR). FCR is defined as, "the fear, worry, or concern about cancer

returning or progressing" (Lebel, Ozakinci, et al., 2016). FCR is consistently identified as a top concern by both cancer survivors (Armes et al., 2009; Baker et al., 2005) and their caregivers (Sklenarova et al., 2015). In a pioneering paper, Lee-Jones and colleagues described FCR as a multifaceted experience with cognitive (e.g., perceptions of risk, beliefs about cancer), emotional (e.g., worry, hypervigilance), and behavioural (e.g., body checking, limited future planning, reassurance seeking) components (Lee-Jones et al., 1997). Since then, numerous theoretical models of FCR have been proposed (Fardell et al., 2016; Lebel et al., 2018; Mellon et al., 2007; Simonelli et al., 2017) and a robust body of research has examined the assessment, prevalence, course, and determinants of FCR in adult survivors and their caregivers (Crist & Grunfeld, 2013; Koch et al., 2013; Simard et al., 2013). While some degree of FCR is to be expected, approximately 50% of adult survivors experience FCR at moderate-to-high levels (Simard et al., 2013), which is associated with increased psychological distress (Simard et al., 2010), poorer quality of life (van den Beuken-van Everdingen et al., 2008), and more emergency and outpatient medical visits (Champagne et al., 2018; Lebel et al., 2013). Females, younger survivors, and caregivers seem to be high risk groups for elevated FCR (Simard et al., 2013). Several validated measures exist to measure FCR in adult survivors, however the Fear of Cancer Recurrence Inventory (FCRI) is the most widely studied and used (Thewes et al., 2012). Longitudinal research has demonstrated that trajectories of FCR are generally stable over time (Simard et al., 2013). Thus, if unaddressed, elevated FCR can be a costly and debilitating issue that affects survivors and their caregivers for the rest of their lives.

Almost all FCR research to date has focused on adult cancer survivors, with some recent consideration of older adolescent and young adult survivors (>18 years) (Sun et

al., 2019; Yang et al., 2016) and adult survivors of childhood cancer (Kelada et al., 2019; McDonnell et al., 2021). There is emerging qualitative (Heathcote et al., 2021; Wakefield et al., 2010, 2011; Weigers et al., 1998) and quantitative (Cunningham et al., 2021; Koutná et al., 2021; Peikert et al., 2021; Wroot et al., 2020) evidence that FCR is also a concern for child survivors and their parents, albeit with some unique cognitive (e.g., understanding of illness, autobiographical memory, metacognition) and social (e.g., parent-child relationship, identity development, future orientation) considerations specific to the early experience of cancer (Tutelman & Heathcote, 2020). A significant challenge limiting the advancement of research on FCR in child survivors is the lack of a validated measure for the pediatric population (Tutelman & Heathcote, 2020). Existing studies examining FCR in child survivors have used single item measures that may not adequately capture the construct (Koutná et al., 2021) and adult questionnaires that have not been validated for use with children (Cunningham et al., 2021; Wroot et al., 2020).

1.6. Pain and Fear of Cancer Recurrence

Due to the profound impacts that FCR can have on survivors' lives, significant efforts have been put towards identifying triggers of FCR. Theories of FCR highlight two main categories of triggers – those that are internal (e.g., physical symptoms) and those that are external (e.g., medical appointments, anniversaries) (Fardell et al., 2016; Lebel et al., 2018; Simonelli et al., 2017). There is growing recognition that physical symptoms, particularly pain, may be strong triggers of FCR (Hall et al., 2019; Simard et al., 2013). In adult survivors, more severe bodily pain has been linked with higher FCR (Janz et al., 2011; van den Beuken-van Everdingen et al., 2008), and in adult survivors of childhood cancer, greater information needs related to pain have been associated with greater FCR

(Kelada et al., 2019). To date, one quantitative study has examined the relationship between pain and FCR in child survivors. Out of 10 physical symptoms, survivors reported being most concerned about pain as a potential sign of recurrence (Cunningham et al., 2021). Indeed, pain is an embodied sensation that serves an important evolutionary function; it is an internal "warning system" that alerts an individual to actual or potential bodily threat (Eccleston & Crombez, 1999). Because of the innate relationship between pain and cancer (Twycross et al., 2015) and its evolutionary function as a signal of threat (Eccleston & Crombez, 1999) it is logical that survivors would fear pain as a sign of recurrence. That said, there are many reasons other than cancer recurrence as to why survivors may experience pain after cancer. In addition to those related to cancer and its treatment (outlined in section 1.3), pain is also a natural consequence of living a healthy and active life. Cause(s) of pain can be uncertain and it can be difficult for survivors to discern whether pain that occurs is benign or cause for concern. While pain plays a central role in the everyday lives of survivors of childhood cancer, and is theorized to be a key trigger of FCR, no studies to date have empirically examined the relationship between pain and FCR, nor the role of pain as a predictor of FCR in this population.

1.7. Theoretical Basis (Cancer Threat Interpretation Model)

A particularly relevant theoretical model for understanding pain in cancer survivorship is the Cancer Threat Interpretation (CTI) model (Heathcote & Eccleston, 2017). Drawing from cognitive-affective models of pain (Eccleston & Crombez, 1999; Vlaeyen & Linton, 2000) and somatic interpretation (Cioffi, 1991), the CTI model posits that cancer survivors may be primed to negatively interpret somatic sensations, such as pain, as a threatening sign of disease recurrence. Survivors may therefore become

hypervigilant to signals of pain, making it more frequent and interrupting in their everyday lives. Several cognitive (e.g., biased attending, threat interpretation, catastrophizing) and affective (e.g., anxiety, distress) factors are presented in the model that may be especially important in survivors' experience of pain. In addition, the CTI model proposes that factors related to the survivor's cancer history (e.g., whether pain was a symptom that led to diagnosis) and current context (e.g., what is the nature of the current pain) are likely important to how pain is interpreted. According to the CTI model, survivors' negative interpretations of pain may drive behaviors to alleviate their FCR such as excessive healthcare seeking for reassurance or healthcare avoidance, both of which can impact survivors' long-term physical and psychological wellbeing.

The studies that comprise this dissertation are among the first to examine experience of pain in childhood cancer survivorship and its potential relationship with FCR. While not addressed in the CTI model, the broader pain literature emphasizes that pediatric pain is experienced within the broader family context and highlights the vital role of parents. Drawing on the CTI model and the broader pain and psychology literatures, this dissertation takes a multi-informant (e.g., children and parents) and multi-method (e.g., qualitative and quantitative) approach to examine the experience of pain in survivors of childhood cancer.

1.8. Methodological Considerations

The sections below offer an overview of the key methods used in this dissertation including multimethod research as an overarching method, qualitative inquiry, and experimental pain. The benefits of each method and rationales for its use are discussed. The novel integration of patient engagement within the dissertation is reviewed.

1.8.1. Multimethod Research

This dissertation employed multiple methods (also known as "multimethod research") to obtain a comprehensive understanding of the experience of pain after childhood cancer. Multimethod research occurs when a series of independent but interrelated research studies using different qualitative and/or qualitative approaches are used to answer an overarching research question, topic, or program of research (Morse, 2003). Studies in multimethod designs are complete in and of themselves and the findings are integrated after their completion when broader implications are being made (Johnson et al., 2007). Conversely, mixed methods research occurs when two or more different research approaches are incorporated in a *single* study and findings are integrated (or 'mixed') within the study (Anguera et al., 2018; Johnson et al., 2007).

A key strength of multimethod research is that it allows researchers to examine phenomena from different perspectives (Morse, 2003; Sandelowski, 1995). This was described by Morse (2003) as providing researchers with different levels of data that, taken together, offer a more complete picture of a given phenomenon than each would on its own. A major strength of the current dissertation is its use of multiple methods to examine the overarching research question – what is the experience of pain in survivors of childhood cancer? Together, the methods used in the studies that comprise this dissertation, including individual-level lived experience data and group-level experimental pain and questionnaire data, paint a rich and comprehensive picture of pain after childhood cancer.

1.8.2. Qualitative Methods

Qualitative research refers to a family of methodologies that focus on understanding the meaning and interpretation of experience (Willig, 2017). Qualitative research is not a homogenous method; there are numerous qualitative traditions, such as phenomenology (Moustakas, 1994), grounded theory (Charmaz, 2014), ethnography (Wolcott, 2008), qualitative description (Sandelowski, 2000), and arts-based approaches (Harrison, 2002) that can be paired with various methods of analysis (e.g., thematic analysis (Braun & Clarke, 2006), content analysis (Hsieh & Shannon, 2005)). Each qualitative approach comes with its own theoretical basis, philosophical assumptions, methodological techniques, strengths, and limitations (Creswell, 2007).

Qualitative research is often described as a method that seeks to understand the process of how experience is constructed. That is, the "what", "how", and "why" of experience (Ormston et al., 2014). Other questions, such as "how much" are best answered by positivist approaches (i.e., quantitative research). Qualitative research relies on distinct epistemological and ontological assumptions - in other words, ideas about what knowledge and reality are and how they can be understood (Creswell, 2007). Quantitative research is largely founded on the assumption that there is a single, objective reality that can be observed or measured, though many quantitative research acknowledge the inability to prove something in a final sense. Conversely, qualitative research operates on the belief that there is no one absolute truth, but rather a narrative truth that is based on context (Ormston et al., 2014; Yilmaz, 2013). In this way, qualitative research is inherently reflexive, meaning that the researcher approaches the data with their own beliefs, ideas, and preconceptions that inevitably shape data collection and analysis

(Ormston et al., 2014). While positivist approaches generally view researcher bias as a weakness, qualitative research sees reflexivity as an inherent and unavoidable part of the construction of knowledge, and something that adds richness to the data and interpretation (Ben-Ari & Enosh, 2011; Finlay, 2002; Lynch, 2000). Due to the difference in logic regarding what knowledge is and what it represents, traditional positivist criteria relating to aspects of research quality such as validity, reliability and sample size are not relevant to qualitative research (Eakin & Mykhalovskiy, 2003; Sandelowski, 1993). Instead, distinct criteria such as trustworthiness, theoretical and conceptual insight, and credibility are used as indicators of quality (Eakin & Mykhalovskiy, 2003; B. Smith, 2018; Tracy, 2010).

Qualitative research is ideally suited for the study of pain. Pain, by definition, is a personal, subjective and multidimensional experience (Raja et al., 2020). Yet, the vast majority of pain research to date has relied on single numerical reports of patients' pain (e.g., pain intensity on a numerical rating scale) that do not capture the complexity of the experience. Instead, qualitative research can facilitate rich exploration of the meaning and experience of pain in ways that are inaccessible to other research methods (Osborn & Rodham, 2010; Tutelman & Webster, 2020). Despite the promise it holds, qualitative research has been underrepresented in pain research relative to quantitative approaches (Osborn & Rodham, 2010; Tutelman & Webster, 2020). Qualitative research cannot and should not replace quantitative pain research methods. Instead, the latter provides complementary data that can enhance quantitative findings (Osborn & Rodham, 2010). The current dissertation harnesses the potential of qualitative methodology to obtain a rich, in-depth understanding of pain after childhood cancer.

1.8.3. Quantitative Sensory Testing

Quantitative Sensory Testing (QST) refers to a set of non-invasive experimental procedures that systematically assess perceptual responses to standardized sensory stimuli. The overarching goal of QST is to assess the functioning of sensory and pain pathways (Backonja et al., 2013). QST offers numerous advantages over other experimental pain paradigms commonly used in pain research (e.g., the cold pressor task) due to the array of modalities that can be tested, the precise calibration of stimuli, and the availability of standardized protocols with normative reference values (e.g., the German Neuropathic Pain Research Network protocol (Rolke et al., 2006)), including those specific to children (Blankenburg et al., 2010; Meier et al., 2001; van den Bosch et al., 2017). The use of QST began with the assessment of adult peripheral neuropathies. Since then it has been used to evaluate somatosensory and pain functioning in a range of disorders with impacts on the nervous systems (Backonja et al., 2013; Martland et al., 2020; Uddin & MacDermid, 2016). One of the greatest clinical utilities of QST has been its role in phenotyping patients based on patterns of sensory loss, gain, and pain hypersensitivity. This has moved the pain field towards targeted and mechanism-based diagnoses and treatments (Baron et al., 2017; Cruz-Almeida & Fillingim, 2014; Maier et al., 2010). QST has also been used as a method to examine intervention efficacy (Grosen et al., 2013) and as an experimental pain induction technique (Cruz-Almeida & Fillingim, 2014).

QST measures assess the functioning of distinct sensory specific small (Aδ and C) and large (Aβ) peripheral fibres as well as their corresponding pathways in the broader central nervous system (Backonja et al., 2013). Stimuli used in QST protocols fall within

two major categories: thermal (e.g., cool, noxious cold, warm and noxious hot) and mechanical (e.g., touch, pressure, and vibration) stimuli. Comprehensive QST protocols generally evaluate detection thresholds (i.e., the intensity at which a stimulus is detected), pain thresholds (i.e., the intensity at which a stimulus is perceived to be painful) and measures of temporal summation (i.e., the increase in pain intensity due to repetitive noxious stimulation) using different stimuli as these tests evaluate the functioning of distinct pathways (Hermann, 2013). For instance, the sensation of cool and noxious cold rely on the activation of Aδ and C fibres, respectively. Warm and noxious heat stimuli activate C fibres and mechanical stimuli depend on the activity of Aβ, Aδ, and C-fibres (Walk et al., 2009). QST findings are associated with clinical outcomes (e.g., more sensitivity on QST is linked with greater pain and disability) (Georgopoulos et al., 2019) and biopsychosocial factors (e.g., individuals with worse psychosocial functioning display greater sensitivity on QST tests) (Wallin et al., 2012).

While QST has been used extensively in adult pain research for several decades, it has been more recently applied to pediatric populations (Hermann, 2013). QST is considered to be feasible in children as young as 6 years of age (Blankenburg et al., 2010), though thermal detection thresholds have also been measured in children as young as 4 years old (Dua et al., 2019; Hilz et al., 1996). The application of QST to children requires unique considerations. For instance, QST studies in samples of healthy children have found that somatosensory functioning matures across childhood and is dependent on both age and sex, with girls (Blankenburg et al., 2011) and younger children (Blankenburg et al., 2011; Hirschfeld et al., 2012) displaying more sensitivity. Additionally, as psychophysical tests, QST measures are sensitive to contextual

influences such as attention, concentration and reaction time (Cruz-Almeida & Fillingim, 2014; Hermann, 2013) which are factors still developing in childhood. Nevertheless, QST measures have demonstrated good test-test and interrater reliability in children (Hilz et al., 1996; Nikolajsen et al., 2011; Soee et al., 2013; Thibault et al., 1994); however this is an ongoing area of inquiry (Hermann, 2013). Overall, use of QST has great value in furthering our understanding of pain and sensory processing in childhood cancer survivors – a population at high risk for changes to somatosensory function.

1.8.4. Patient Engagement

The patient engagement movement represents one of the most major recent advancements in the health research. Patient engagement, also known as "patient and public involvement" or "stakeholder engagement" (Manafo et al., 2018) refers to the "meaningful and active collaboration in governance, priority setting, conducting research and knowledge translation" (Canadian Institutes of Health Research, 2019). In the context of patient engagement, patients are defined broadly including not only individuals with personal lived experience of a health issue, but also their informal caregivers including family and friends (Canadian Institutes of Health Research, 2019). Patient engagement represents a fundamental paradigm shift in the research enterprise by moving beyond solely involving patients at the level of research participants, to actively *partnering* with patients as expert members of research teams. Patient engagement exists on a spectrum, ranging from informing and consulting on research, to being involved as collaborators, and project leads (International Association for Public Participation, 2018; Vat et al., 2017). More distal forms of patient engagement (i.e., informing and consulting) are most common (Domecq et al., 2014); however, there is consensus that

patient engagement is more meaningful and impactful when patient partners are more actively and proximally involved (Black et al., 2018; Hamilton et al., 2017). Patients can be engaged at all stages of research, from prioritizing research questions, to grant writing, study design, participant recruitment, data collection, analysis, and dissemination (Duffett, 2017).

The rationale for patient engagement in research is compelling (Vat et al., 2020). There is building evidence that when patients are engaged in research, research is more relevant, usable, and accessible (de Wit et al., 2014; Dudley et al., 2015), study designs are more appropriate and sensitive (Crocker et al., 2017; Mann et al., 2018), and there is more effective participant recruitment and retention (Ennis & Til, 2013; Iliffe et al., 2013; Levitan et al., 2018). Studies incorporating the principles of patient engagement result in better uptake of research evidence (Borup et al., 2016; Levitan et al., 2018) leading to less research waste (Minogue et al., 2018). That said, meaningful engagement of patients in research requires increased time, effort, and resources from the research team (Blackburn et al., 2018; Rouleau et al., 2018). While patient engagement is associated with considerable financial value (e.g., more effective and rapid data collection, reduced number of protocol amendments) (Levitan et al., 2018), there are also upfront costs to researchers (e.g., compensation of patient partners) (Rouleau et al., 2018). Nevertheless, the number and significance of the benefits are believed by many to outweigh the costs (Vat et al., 2020). Numerous curricula (Bell et al., 2019; Macarthur et al., 2021) and guidelines on best practice (Richards et al., 2018, 2020) have been designed to train researchers and patients on the practice of patient engagement and to help facilitate its integration across all areas of research. The current thesis employed the principles of

meaningful patient engagement (Black et al., 2018; Hamilton et al., 2018) across all studies including the novel engagement of a patient partner as a member of the thesis committee.

1.9. Introduction to Dissertation Papers

Overall, the present dissertation sought to advance the literature on pain in childhood cancer survivors. Specifically, this dissertation aimed to: 1) qualitatively explore the meaning of experience of childhood cancer from the perspectives of survivors and their parents; 2) examine, using a laboratory-based QST protocol, generalized differences in pain and sensory functioning in childhood cancer survivors compared to reference values; 3) adapt and validate self-report measures of FCR for childhood cancer survivors and their parents; and 4) examine the contributions of pain, anxiety and pain catastrophizing to FCR in childhood cancer survivors and their parents. These aims are addressed in four separate papers (Chapters 2-5). A general discussion of the results, their theoretical and clinical implications, and overall strengths and limitations is presented in Chapter 6.

The first study, outlined in Chapter 2, was a qualitative examination of the meaning and experience of pain after childhood cancer. While pain plays a central role in the diagnosis and treatment of cancer, a crucial gap in the literature is how children experience make sense of their pain in survivorship (Alberts et al., 2018). The first study in the present dissertation addressed this gap. There was no specific hypothesis for this study since qualitative research is not intended to test hypotheses. However, the aim was to gather rich data to illuminate childhood cancer survivors', and their parents', experiences of pain and the meanings they attribute to pain after cancer treatment. Child

cancer survivors and their parents were recruited to participate in separate in-depth interviews. Data were collected and analyzed using Interpretive Phenomenological Analysis (IPA) (J. A. Smith et al., 2009).

The second study, outlined in Chapter 3, was a laboratory based QST study that examined generalized differences in pain and sensory processing in survivors of childhood cancer compared to age- and sex-matched reference values. A standardized QST protocol for children that comprehensively examines thermal and mechanical detection and pain thresholds and pain sensitivity at the right thenar eminence was used (Blankenburg et al., 2010). Demographic, clinical, and psychosocial factors and their relationship to survivors' pain and sensory processing were also examined. The use of an experimental pain paradigm with a diverse sample of survivors overcomes the limitations of past research on pain in childhood cancer survivors which has largely relied on questionnaire-based methods to assess pain. A total of 56 survivors of childhood cancer between the ages of 8-17 years attended an in-lab session where they completed questionnaires assessing their psychosocial functioning and participated in the QST protocol. Survivors' QST data was compared to age- and sex-matched reference values (Blankenburg et al., 2010). It was hypothesized that survivors of childhood cancer would exhibit altered pain and sensory detection thresholds across the QST parameters examined compared to the reference values.

The third study, outlined in Chapter 4, describes the development and validation of a self-report measure to evaluate FCR in survivors of childhood cancer and their parents. There is growing interest in the study of FCR in child cancer survivors (Tutelman & Heathcote, 2020), including its relationship with pain. However, progress in

the field has been hindered by the lack of a validated measure to assess FCR in children and their parents. In this study, the FCRI (Simard & Savard, 2009) – the most well-studied and widely used measure of FCR in adults (Thewes et al., 2012) – was adapted for use with childhood cancer survivors ages 8-18 years, the Fear of Cancer Recurrence Inventory – Child version (FCRI-C) and their parents, the Fear of Cancer Recurrence Inventory – Parent version (FCRI-P). The adult measure was adapted for children through a rigorous process of expert panel input and cognitive interviews (Bowen et al., 2004). The wording of the original adult measure was also modified to be appropriate for parents. The psychometric properties of the adapted measures were examined as were their relationships with measures of construct and criterion validity. Data for the current study were collected at multiple sites; participants were those who participated in Study 2 in addition to participants who were recruited through two additional children's hospitals in North America.

The fourth and final study, outlined in Chapter 5, was a theory-driven, questionnaire-based study examining the relationship between trait anxiety, child pain intensity, pain catastrophizing, and FCR in childhood cancer survivors and their parents. While a theoretical link suggests that anxiety, child pain, pain catastrophizing, and FCR are implicated in a maladaptive cycle in survivors of childhood cancer (Heathcote & Eccleston, 2017), the relationships between these variables have not been examined. It was hypothesized that (1) trait anxiety, child pain intensity, pain catastrophizing and FCR would be significantly correlated in children and parents; and (2) pain catastrophizing would explain unique variance in FCR over and above trait anxiety and pain intensity for children and parents. Participants were the children who participated in the study outlined

in Chapter 3 and an accompanying parent. As mentioned above, past research on FCR and pain in survivors of childhood cancer have used non-validated measures. This study intentionally addressed this limitation by employing valid and reliable tools to assess FCR (the FCRI-C and FCRI-P developed in the study in Chapter 4) and child pain (the Pain Questionnaire) (Palermo et al., 2004).

CHAPTER 2: WHEN "A HEADACHE IS NOT JUST A HEADACHE": A QUALITATIVE EXAMINATION OF PARENT AND CHILD EXPERIENCES OF PAIN AFTER CHILDHOOD CANCER

The manuscript based on this study is presented below. Perri Tutelman, under the supervision of Dr. Christine Chambers, was responsible for developing the research question, methodology and analytic approach, and obtaining ethical approval, and funding. She developed the study protocol and collected the data. Ms. Tutelman was the lead on data analysis and interpretation, with the support of her co-authors, and wrote the initial draft of the manuscript. Prior to submission, she received and incorporated feedback from the study's co-authors. The manuscript underwent peer-review and Ms. Tutelman led the relevant revisions. The manuscript was accepted for publication in *Psycho-Oncology* on June 30, 2019. The full reference for this manuscript is:

Tutelman, P. R., Chambers, C. T., Urquhart, R., Fernandez, C. V., Heathcote, L. C., Noel, M., Flanders, A., Guilcher, G. M. T., Schulte, F., Stinson, J. N., MacLeod, J., & Stern, M. (2019). When "a headache is not just a headache": A qualitative examination of parent and child experiences of pain after childhood cancer. *Psycho-Oncology*, *28*(9), 1901–1909. https://doi.org/10.1002/pon.5170

2.1. Abstract

Objective: Today over 80% of children diagnosed with cancer are expected to survive. Despite the high prevalence of pain associated with the diagnosis and treatment of childhood cancer, there is a limited understanding of how having cancer shapes children's experience and meaning of pain after treatment has ended. This study addresses this gap by exploring childhood cancer survivors' (CCS') experiences of pain from their perspective and the perspective of their parents.

Methods: Twenty semi-structured interviews were completed with CCS (50% female; mean age = 13.20 years, range = 8-17 years) and their parents (90% mothers). Data were analyzed using Interpretive Phenomenological Analysis.

Results: Analyses revealed three superordinate themes present in the data: (1) pain is a changed experience after childhood cancer; (2) new or ambiguous pains may be interpreted by CCS and parents as a threat of disease recurrence, late effects, or a secondary cancer; and (3) pain interpretation occurs within the broader context of how CCS and parents appraise their cancer experience. Parents generally appraised their child's cancer and pain as more threatening and were influential in guiding their child's interpretations.

Conclusions: The cancer experience played an important role in shaping CCS' and their parents' experience and interpretation of pain in survivorship. This study provides novel data to inform the development and refinement of new and existing conceptual models of pain and symptom perception after cancer. The results also point to key areas for future investigation and clinical intervention to address the issue of pain in cancer survivorship.

2.2. Introduction

Pain is a unique sensory and emotional experience that functions to alert of bodily threat and avoid harm (Eccleston & Crombez, 1999). Pain as a signal of threat is particularly salient in the context of childhood cancer. For many children, pain was an initial symptom that resulted in a cancer diagnosis (Jonsson et al., 1990; Miser et al., 1987; Reulecke et al., 2008). Unfortunately, pain continues over the course of a child's treatment with almost all children reporting pain as a consequence of skin-breaking procedures, chemotherapy, and/or radiation (Ljungman et al., 2000; Pöder et al., 2010; Van Cleve et al., 2004).

Today more than 80% of children diagnosed with cancer are expected to survive (Ward et al., 2014). Nevertheless, childhood cancer survivors (CCS) are at risk for late effects of treatment (Dickerman, 2007), and must be vigilant for signs of recurrence or a secondary cancer (Bhatia & Sklar, 2002). Despite the central role of pain in the diagnosis and treatment of childhood cancer, the pain experience in the survivorship period has received relatively little attention (Alberts et al., 2018). Emerging work in this area suggests that pain may be a frequent occurrence and may impact survivors' physical and psychological functioning (Jensen et al., 2010; Lu et al., 2011; Tutelman et al., 2018). The recently proposed Cancer Threat Interpretation (CTI) model highlights psychosocial factors which may be associated with pain in cancer survivorship. The CTI posits that cancer survivors may be more likely to negatively interpret pain as a threatening sign of disease recurrence, and thus be hypervigilant to signals of pain, making pain more common and interrupting in their everyday lives (Heathcote & Eccleston, 2017). In the context of childhood cancer, parents are likely to play an important role, as they have also

reported fears of what somatic sensations may represent for their children who have survived cancer (Heathcote & Eccleston, 2017). These factors are consistent with theories that highlight the important role of cognitive and affective factors in pain perception (Eccleston & Crombez, 1999). There is strong evidence to support that an individual's experiences of pain can be altered by variables such as their cognitions and affect (Woo, 2010), past pain experiences (Weisman et al., 1998), social and family interactions (Caes, Goubert, et al., 2014; Cline et al., 2006), pain memories (Chen et al., 2000; Noel et al., 2017), and the threat level of pain (Boerner et al., 2016). Given the nature of the disease and its treatment, cancer-related pain may be associated with significant distress (Penner et al., 2008), feelings of uncertainty (Fortier et al., 2013), and threatening thoughts of mortality (McCaffrey, 2006). Cognitive-affective models of pain posit that these factors would have a powerful, lasting influence on how CCS experience and interpret pain in their everyday lives (Eccleston & Crombez, 1999; Holley et al., 2016; Ryckeghem et al., 2019). Yet, there is a limited understanding of how having cancer shapes children's meaning of pain after treatment has ended. The purpose of this study was to explore CCS' experiences of pain from their perspectives and the perspectives of their parents.

2.3. Method

2.3.1. Study Design

The current study used in-depth semi-structured interviews guided by the theoretical foundations of Interpretive Phenomenological Analysis (IPA). IPA is a qualitative framework that seeks to understand human lived experience and the meaning that individuals ascribe to their experiences (J. A. Smith et al., 2009).

2.3.2. Participants

Participants were recruited from the IWK Health Centre's pediatric hematology/oncology database. CCS between the ages of 8-18 were eligible to participate if they were previously diagnosed with any cancer, completed cancer-related treatment, and had not experienced a recurrence or a secondary cancer. CCS also had to have one parent/guardian willing to participate. CCS were eligible regardless of their pain status post-treatment. Ten families were purposively recruited to participate, resulting in a total of 20 participants (see Table 1 for demographic characteristics). This sample size is consistent with best practices in IPA research given its idiographic focus (J. A. Smith et al., 2009). To achieve the intended sample size of 10 families, a total of 26 families were approached. Reasons for non-participation included being unable to reach families to schedule interviews (n=12) and families expressing that they were not interested in participating (n=4). The study protocol was approved by the institutional Research Ethics Board (#1022845).

2.3.3. Data Collection

CCS and parents individually took part in semi-structured interviews. Within each dyad, parent interviews were conducted first. Interview schedules with open-ended questions were developed by the research team and guided the interviews (see supporting information). One investigator (PT) conducted all interviews. Informed consent/assent was obtained from all parent/child participants prior to each interview. Interviews were audio-recorded and transcribed verbatim.

2.3.4. Data Analysis

The data were analyzed using IPA according to standard procedures (J. A. Smith et al., 2009). IPA emphasizes the active role of the researcher in the research process, with analysis and interpretation taking part in a two-staged ("double hermeneutic") process. That is, as participants reflect on and attempt to make sense of their worlds, the researcher tries to make sense of the participants making sense of their worlds (J. A. Smith et al., 2009). First, transcripts were read several times to gain a detailed understanding of each participant's account. Initial exploratory notes were made highlighting salient discourse. Moving from a descriptive to an interpretive level of analysis, transcripts were then coded with emergent themes through line-by-line analysis. The aforementioned steps were completed for each transcript before moving to the next. Emergent themes identified in earlier transcripts were used to inform the coding of subsequent transcripts and as new themes emerged, earlier transcripts were revisited to determine if they applied. This process was completed twice, once for the group of parent transcripts and once for the group of child transcripts. Abstraction was used to cluster emergent themes from the transcripts into superordinate themes that captured parent and child experiences. The analysis was led by the first author (PT), who closely and iteratively went back to the transcripts and primary data to constantly check her own sense-making against what the participants actually said, helping ensure her interpretations reflected participants' lived experiences and meanings. At each step, the analysis was also audited by a second author who is highly experienced in IPA (RU) to ensure that the results were grounded in the data.

2.4. Results

The analyses revealed three interrelated superordinate themes (Figure 1).

2.4.1. Theme 1: A Changed Experience of Pain

Almost all CCS and their parents reflected on how their perception of painful sensations had changed after cancer. Some CCS and their parents denied any regular pains and others reported experiencing pain on a frequent (weekly or daily) basis. Commonly reported pains included musculoskeletal pain, headaches, and abdominal pain. While some of these pains were attributed to "everyday causes" (e.g., pain from exercise, food intolerance, menstrual cramps etc.), many were tied to CCS' past cancer experiences, including the long-term effects of cancer or its treatment. For children diagnosed and treated at a young age, parents played an important role in comparing their pre- and post-cancer experiences.

> *"[Son] has compression fractures which will never fully heal. So he often has pain in his back from that. His arm is sore as well. Like he'll often say, 'my arm is bothering me tonight.'" (Mother of CCS, age 10)*

Additionally, some CCS described a decrease in their ability to perceive pain due to chemotherapy-induced nerve damage.

> *"Growing up there was less pain …I don't actually know why but it must have been something with all the drugs I had … there's a big problem with it because if I get hurt, I don't know how hurt I actually am." (CCS, age 16)*

Others noticed an increase in their tolerance for pain. Many CCS and their parents expressed that the intensity and frequency of pain experienced during treatment has made many pains experienced in survivorship feel insignificant in comparison.

"… Pain is so different for her… I mean when you have your abdomen cut open and all your organs taken out, when you get a splinter, it's no big deal." (Mother of CCS, age 11)

2.4.2. Theme 2: Pain as a Threat

Central to the experience of pain in cancer survivorship was the idea of pain as a sign of bodily threat. Almost all CCS described instances where they interpreted bodily pain as a potential indication of their cancer recurring. This seemed to occur most often in the context of new or ambiguous painful sensations. CCS expressed that when they are unable to assign an explanation to a pain, they begin to wonder whether the pain could be a sign of their cancer returning.

"…Most of the time I know what it is. But like if it's a pain that I've never gotten before then I'll worry about it." (CCS, age 15)

Parents seemed to play a crucial role in CCS' appraisal of their bodily pain. CCS reported that they consult with their parents when experiencing a new or ambiguous pain to get their help with finding an explanation. Parents expressed that they are generally 'in tune' with their child's body and seemed familiar with their child's common pains and associated causes. However, learning about a new or ambiguous pain often triggered parents to assiduously evaluate its nature and cause, and for some, led them to seek medical attention (via doctor's appointments or emergency room visits).

"…That's the first thought – is this just the everyday normal or is this something more? I'm probing around to say like … 'where's it sore? And how long has it been sore? Was it just today or is it sore like this everyday?'

It's always the first thing that you think of – 'Oh my gosh, is there something more?'" (Mother of CCS, age 10)

CCS reported that they rely heavily on their parents' responses to guide their own interpretation of the pain as threatening or benign. This was important, because overall, parents seemed to be more alarmed by pain and what it could represent than CCS.

"I sometimes worry that the pain in my legs means [my cancer is back]. And then I'm scared. But then I ask my mom … and it depends on what she says. And then I say, 'okay' or, 'yikes' or, 'whatever'." (CCS, age 8)

Parents' and CCS' tendency to interpret pain as a sign of disease recurrence seemed to be especially relevant if pain was a symptom that preceded the child's cancer diagnosis.

"[Son] has been having mild headaches the last couple of days. And you know, that's how it all started 10 years ago … so a headache is not just a headache …" (Father of CCS, age 17)

However, this was not universally true for all CCS. Some CCS who were diagnosed at an age too young to remember (i.e., infancy) also endorsed threatening thoughts about pain.

Threatening appraisals of pain in survivorship were not limited to the possibility of pain representing a cancer recurrence. In addition, CCS and their parents also reported feeling concerned that new or ambiguous pains could be a sign of a secondary cancer or late effects of their cancer treatments, which may have serious implications. This was particularly relevant for survivors of cancers where curative surgery was possible (e.g., Wilms Tumor, Hepatoblastoma).

"She had an episode that no one could really explain of severe abdominal pain. .... that episode scared us all, because [the pain] was right above her liver… we all panic about rejection still. And we were all thinking, you know, 'Is she rejecting her liver'… 'What's happening here?'" (Mother of CCS, age 16)

2.4.3. Theme 3: Appraisal of the Cancer Experience

CCS' and parents' perceptions of pain in survivorship seemed to occur within the broader context of the meaning they attached to their cancer experience. Overall, CCS seemed to appraise their experiences through a relatively neutral, objective lens. Conversely, parents' appraisals of their child's cancer seemed to be more threatening and emotionally-charged. The valence of the meaning that both CCS and their parents assigned to their cancer experience seemed to influence how they appraised pain, other symptoms, and their overall functioning.

Most CCS reported having very few detailed memories of their cancer and treatment. The memories they did describe, including the painful aspects of treatment, were generally recalled in a rational, matter-of-fact manner.

"There were 30 doses of chemotherapy and I had to get a body cast, which was for the MRI machine. And I would have to lay perfectly still so they could get good pictures. It was pretty tough in the beginning … but I got used to it." (CCS, age 17)

The pragmatic way that CCS' viewed their cancer experience seemed to extend to how they appraised their health and self-concept in survivorship. Most CCS viewed their current lives as being consistent with their same-age peers. Many CCS seemed to be

content with their ability to participate in everyday activities (e.g., school, extra-curricular activities) that cancer seemed to simply be an event they experienced. They reported that thoughts about cancer were generally not present or interfering in their everyday lives, even despite the presence of some differences (e.g., hearing loss, physical appearance). CCS reported that when thoughts about cancer do appear, they tend to be transient in nature and neutral in valence.

> *"[Life] is good… I'm pretty much back to normal …I don't think about [when I had cancer] a lot. I mean sometimes it will just pop in my head and I'll be like,' oh, yeah, right.' But yeah, I don't really think about it much …" (CCS, age 15)*

Similarly, CCS also seemed to appraise their current health status in a pragmatic, objective way. Most CCS admitted having some concerns about their health and the future. However, they described being able to think realistically to balance these thoughts, and seemed comforted and satisfied by what they knew about their risks for recurrence and other late effects.

> *"… I'm 50% more likely to get lung cancer or breast cancer… I know there's a possibility of [my cancer] coming back but it's never really been like, 'oh, this is going to terrify me for the rest of my life'." (CCS, age 16)*

This perspective seemed to foster feelings of self-efficacy and resilience despite living with pain or other late effects.

> *"Well, occasionally I will have pain in my arm. But only usually if I'm playing games where I have to use my arm. But most times I try and keep*

my arm a little elevated and use my good arm to my advantage." (CCS, age 10)

In contrast to how CCS appraised their experience of cancer, parents seemed to attach a significantly more threatening and emotionally-charged meaning to their child's illness. Parents described vivid and graphic memories of their child's treatment, including the trauma of witnessing their child in pain.

"Honestly I want to throw up right now [thinking back to son's painful procedures during treatment] … it was disgusting. It's awful to hear your child scream … he's not a crier. But it hurt. Everything that he went through hurt…" (Mother of CCS, age 15)

This traumatic appraisal seemed to be rooted in feelings of injustice and in the threat of losing their child. This threat seemed to remain for many parents (to varying degrees) even years after their child completed treatment.

"I mean the first thing that crosses your mind when you hear the diagnosis is 'I'm going to lose my child'. And you never quite lose that … I was diagnosed with PTSD. Those first two years I would wake up with visions of chemo." (Mother of CCS, age 10)

Parents reported playing an active role in their child's health throughout their treatment. This included monitoring their child's symptoms, advocating for their child's care, and coaching their child through painful procedures and applied regardless of the age of the child. These behaviours seemed to be driven by several factors including their responsibilities during their child's treatment, mistrust in the medical system due to

delays in their child's diagnosis and fear of medical errors, and ultimately, an instinctual desperation to do everything in their power to save their child and lessen their suffering.

> *"Port access was hard because it was ripping off the tape. And that was agonizing … I took control of most situations. They would have their way but then I would have my way that I just knew would help her get through it quicker… it traumatized her when they did it because they were nervous and they weren't noticing the cues that I was. So it was just easier if whenever we went to our emergency here or at the hospital that I just did it. And if they had let me do the ports, I would have done that as well." (Mother of CCS, age 11)*

Parents described how this close attention to their child's health does not end once treatment is over; they reported continuing to play an active role in their child's health years into survivorship. This manifested in several ways, including being hypervigilant to their child's bodily symptoms, including pain. This seemed to be especially true for parents with more negative and traumatic appraisals of their child's illness. Parents' responses suggested that there may be a number of reasons for this hypervigilance to their child's bodily symptoms in survivorship. For instance, parents discussed the habit of needing to watch for signs of potentially life-threatening adverse events during treatment, and being on high alert for signs that could turn their world upside-down and threaten their child's life once again (e.g., cancer recurrence, or a serious late effect). While some parents noted that their degree of hypervigilance has decreased over time, it remained present, to varying degrees, for all parents.

"My wife picks up on every little clue. Well, with this latest thing [son's headaches], she said to me, 'He just looks off'. Now what does that mean? She said, 'Well, he's not acting like he normally acts.' ... so yeah, in a family of [a child who had cancer], [we] perceive things differently. And it can be a struggle." (Father of CCS, age 17)

As opposed to CCS who seemed content knowing the facts about their health and risks in survivorship, some parents appeared to struggle with accepting this information. For these parents, the threatening meaning they attached to their child's cancer experience, coupled with their heightened emotion about what their child's symptoms could mean, seemed to override the factual information they knew about their child's health and likelihood of recurrence or late effects.

"I'm more aware of his health now. Even my other two, I'm on them about stuff. I'm still paranoid when he gets the sniffles ... Even though he's okay and he could probably fight it off, I still get really paranoid." (Mother of CCS, age 17)

This tendency to view their child's cancer through a more emotionally-charged lens seemed to contribute to parents' threatening appraisals of their child's pain. Whereas most CCS denied any significant functional impairments, some parents described feeling a grave sense of sadness and helplessness about their child experiencing pain and other limitations in survivorship.

"With [son], just knowing his condition he's probably always going to have these issues. I know that his back is never going to fully heal. He will always

probably have a sore back … he has compression fractures that are probably always going to plague him." (Mother of CCS, age 10)

Parents reflected on the impact of their heightened emotion and awareness to their child's health on their children. Parents acknowledged the relationship between their own hypervigilance and the development of hypervigilance to bodily symptoms in their children.

"[Daughter] is very over-aware. I always got phone calls from school and she would just have to tell me something. I think she always thought that I would want to know because it might be something scary. I was constantly telling her like 'I need to know how much water you drink, you have to tell me if you've thrown up, I need to know everything' … So she thought I had to know everything. And I was glad. But it also made her a very nervous little girl." (Mother of CCS, age 11)

2.5. Discussion

The cancer experience played an important role in shaping CCS' and their parents' experience (theme 1) and interpretation (themes 2 and 3) of pain in survivorship. These results provide preliminary support for key aspects of the CTI model (Heathcote & Eccleston, 2017) in that the presence of ambiguous pains are interpreted as threatening (e.g., pain as a sign of recurrence) and may result in behavioural consequences (e.g., medical investigations). The data also offer several novel extensions to the model. In this study, threatening appraisals of pain in cancer survivorship extended beyond fear of recurrence. Many CCS and their parents expressed fearing that new or ambiguous pains could represent late effects of cancer treatment, and differentiated between pain as a fear

of recurrence versus pain as a fear of a secondary cancer. Further, the CTI model posits that threatening interpretations of pain in cancer survivorship are likely driven by individuals' experiences with pain at diagnosis and during treatment (Heathcote & Eccleston, 2017). While some participants endorsed this, it was not universally true. In fact, the only CCS who had an affective reaction to talking about their interpretation of pain in survivorship was diagnosed and treated in infancy and therefore had no firsthand memories of their symptoms before or during treatment. This speaks to the potential influence of narratives that are created by parents and healthcare professionals, as well as the meaning CCS learn to ascribe to cancer and pain.

CCS' and parents' experiences of pain seemed to occur within the context of how they appraised their cancer experiences. CCS and their parents who held more negative evaluations of their cancer experience, and who had more difficulty tolerating the uncertainty of ambiguous pains, seemed to be more distressed by the presence of pain in survivorship and what it could mean for the present and future. This is consistent with the literature on parent and child illness-related cognitive appraisals (Ramsey et al., 2016; Szulczewski et al., 2017). Illness-related cognitive appraisals, such as illness uncertainty and attitude towards illness, have emerged as key factors associated with child and parent adjustment in pediatric cancer (Fortier et al., 2013; Mullins et al., 2016; Neville et al., 2019). Higher levels of parent and child illness uncertainty and more negative evaluations of illness are associated with poorer parent and child quality of life and psychological functioning (Fortier et al., 2013; Fuemmeler et al., 2001; Maurice-Stam et al., 2008; Mullins et al., 2016) and are positively related to child-reported physical symptoms including pain (Fortier et al., 2013). To date these relationships have been predominantly

explored in children undergoing active treatment. In the current study, there was a striking discordance between parents' and CCS' illness-related cognitive appraisals. While CCS generally held neutral evaluations of their illness, parents' appraisals seemed to be significantly more negative and traumatic in nature. This seemed to differentially impact the degree to which CCS and their parents appraised pain as threatening. This is in line with previous findings suggesting that parents are at higher risk than their children to experience poor psychosocial outcomes after cancer (Kazak et al., 2004), and that parents experiencing emotional distress are more likely to engage in maladaptive thoughts (e.g., catastrophizing) and behaviours (e.g., attending to pain) related to their child's pain (Caes, Goubert, et al., 2014; Caes, Vervoort, et al., 2014). This is important given the known transactional relationship between parent pain behaviors and child pain-related outcomes (Birnie et al., 2016; McMurtry et al., 2010), which was evident in this study.

2.5.1. Study Limitations

Some families invited to participate either did not respond or expressed that they were not interested in taking part. Thus, the families who participated may reflect those with a particular concern or interest in pain or those with a willingness to revisit memories of cancer. While not a limitation per se but rather a characteristic of IPA, it must be recognized that data interpretation may (and will) vary depending on the researcher and his/her prior views and experiences. However, consistent with IPA methods, several steps were taken to ensure that the results were grounded in the data (e.g., an iterative analysis process and an independent audit of the analytic procedures). Also, while IPA does not intend to yield generalizable findings, it should be noted that

the results reflect the experiences of a small number of CCS and their parents with little ethnic diversity.

2.5.2. Research and Clinical Implications

The current results point to unique psychosocial factors (e.g., fear of recurrence) that are associated with pain interpretation in CCS and their parents. However, there are currently no comprehensive, validated measures of fear of cancer recurrence for children, nor are there measures that evaluate fear of pain in the context of cancer survivorship. This study offers novel data to guide the development of measures in these areas. This will allow for the quantitative examination of key research questions, such as characterizing the relationships and interactions between parent and child illness appraisals, trauma symptoms, and pain-related outcomes in CCS. This study alludes to possible associations between these factors, and suggests that they may be involved in facilitating the transfer of pain-related fears in families after childhood cancer. These relationships warrant further investigation and represent potential targets for clinical intervention. Further, larger quantitative studies will be important to characterize the pain experiences in different disease groups (e.g., survivors of pediatric brain tumors), which may reveal significant differences.

The results also speak to the role of clinician communication regarding pain monitoring after childhood cancer. Parents recounted the emphasis that was placed on the need to monitor their child's symptoms, such as pain, while they were on active treatment and acknowledged the difficulty of abandoning this vigilance once their child transitioned off active treatment. This is an area where healthcare professionals can intervene by providing appropriate anticipatory guidance related to pain and symptom monitoring.

This education may be important in preventing pain and other symptom-related fears in the transition from active treatment to cancer survivorship (Heathcote et al., 2018).

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2.7. Conflicts of Interest

There are no conflicts of interest to declare.

2.8. Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

2.9. References

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2.10. Figures

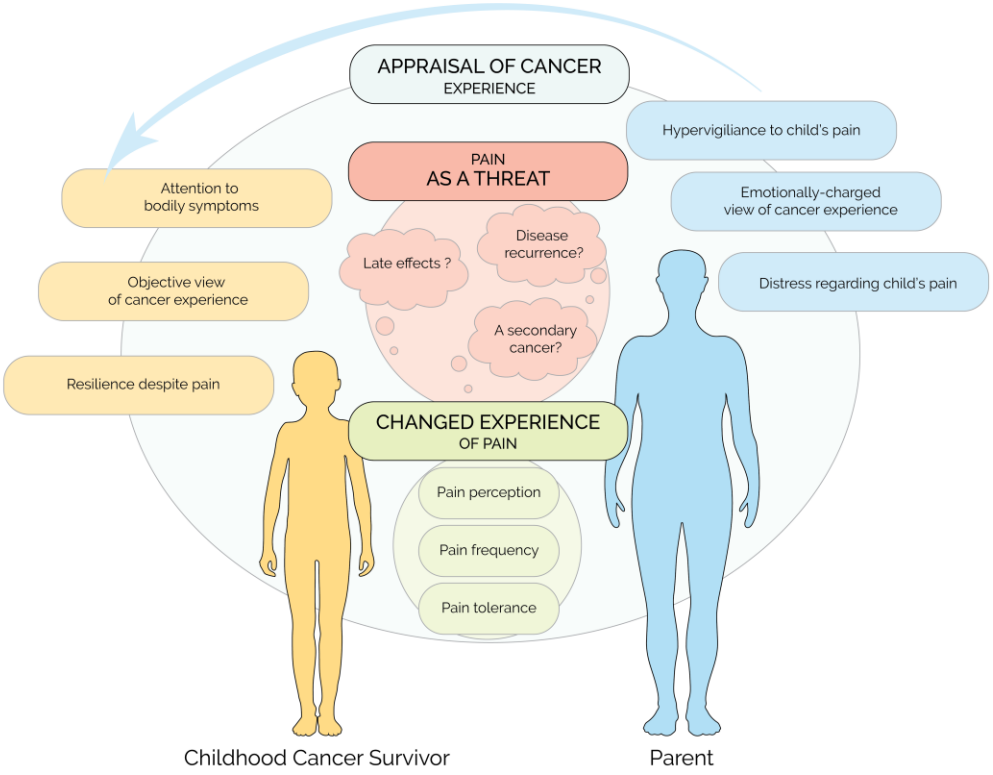

Figure 2.1. The relationship between the superordinate themes describing the experience of pain after childhood cancer.

2.11. Tables

Table 2.1. Participant Characteristics

Characteristic	Mean (SD)	*n* (%)
Child age at interview (years)	13.20 (2.26)	
Range	8-17	
Child sex		
Female		5 (50%)
Male		5 (50%)
Parent relationship to child		
Mother		9 (90%)
Father		1 (10%)
Parent age (years)		
30-49		7 (70%)
50 and older		3 (30%)
Diagnosis		
Brain Tumor		1 (10%)
Hepatoblastoma		1 (10%)
Leukemia (Acute Lymphoblastic)		2 (20%)
Lymphoma		1 (10%)
Neuroblastoma		1 (10%)
Osteosarcoma		1 (10%)
Rhabdomyosarcoma		1 (10%)
Wilms Tumor		2 (20%)
Child age at diagnosis (years)	5.85 (4.53)	
Range	0.5-15	
Time since treatment completion (years)	5.4 (4.50)	
Range	0.67-13	
Child ethnicity		
Caucasian		10 (100%)
Parent ethnicity		
Caucasian		10 (100%)
Child interview length (minutes)	20 (5.27)	
Range	15-32	
Parent interview length (minutes)	42.2 (13.93)	
Range	23-63	

2.12. Supplementary Materials

Supplementary Materials – Appendix A

Sample Questions from the Child Version of the Interview Guide

1. Tell me a little bit about when you were first diagnosed with cancer.
    - *Prompts:* What symptoms did you have?
2. Tell me about the treatments you had for your cancer.
    - *Prompts:* What types of treatments did you have? What do you remember about them?
3. Tell me what you remember about pain you had when you had cancer.
    - *Prompts:* What was the pain from? How often do you think back to the pain you had when you had cancer? What is it like to think back to the pain during that time?
4. Tell me what life is like now that you have finished your treatments.
    - *Prompts:* Are there things that are different for you now (e.g., school, activities)? How often do you think back to your cancer/treatments?
5. Some children worry about their cancer coming back. Is that something that you worry about?
    - *Prompts:* How often? What situations make you think about it?
6. Tell me what it is like when you feel pain in your body now that you have finished treatment.
    - *Prompts:* How often do you have aches/pains? What does it feel like in your body? What is the pain from? How do you know/figure it out? Do you ever worry that the pain might mean something bad?

7. Tell me about a time that comes to mind since you finished treatment when you had an ache or pain in your body.
    - *Prompts:* What thoughts/feelings did you have?
8. When you have pain, what do you do?
    - *Prompts:* What strategies do you use? Who do you tell?
9. Is there anything else that you feel it would be helpful for me to know that we have not yet spoken about?

Note. Interviews were semi-structured. The interview questions were adapted and/or refined depending on the participant. The parent interview guide was modified to capture their perspective (the wording was changed from "you" to "your child).

CHAPTER 3: LONG-TERM ALTERATIONS IN SOMATOSENSORY FUNCTIONING IN SURVIVORS OF CHILDHOOD CANCER

The manuscript prepared for this study is presented below. Perri Tutelman, under the supervision of Dr. Christine Chambers, was responsible for developing the research question, methodology and analytic approach, and obtaining ethical approval and funding. She developed the study protocol and data collection procedures, contributed substantially to data collection, and oversaw staff and volunteers who contributed to these activities. Ms. Tutelman was the lead on data analysis and interpretation, with the support of her co-authors, and wrote the initial draft of the manuscript. Prior to submission, she received and incorporated feedback from the study's co-authors. The manuscript underwent peer-review and Ms. Tutelman led the relevant revisions. The manuscript was accepted for publication in *PAIN* and published online ahead of print on September 25, 2021. The full reference for this manuscript is:

Tutelman, P.R., Chambers, C.T., Cornelissen, L., Fernandez, C.V., Flanders, A., MacLeod, J., Sherry, S.B., Stewart, S.H., Urquhart, R., de Gagne, S., Guilcher, G.M.T., Hashmi, J., Heathcote, L.C., Noel, M., Schulte, F.S.M., Stinson, J.N.& Stern, M. (2021). Long-term alterations in somatosensory functioning in survivors of childhood cancer. *PAIN*. Advance online publication. https://doi.org/10.1097/j.pain.0000000000002486

3.1. Abstract

Cancer and its treatment can have lasting consequences on somatosensation, including pain, which is often underrecognized and undertreated. Research characterizing the impact of cancer on pain and sensory processing in survivors of childhood cancer is scarce. This study aimed to quantify generalized differences in pain and sensory processing in survivors of childhood cancer compared to reference data using a standardized thermal and mechanical quantitative sensory testing (QST) protocol. The association between demographic, clinical (e.g., leukemia versus other cancers, treatment exposures), and psychosocial (e.g., anxiety, pain catastrophizing) variables and sensitivity to pain and sensory stimuli were also evaluated. Participants were 56 survivors of various types of childhood cancer (52% male, M_{age}=13.5 years, *SD*=3.2, range=8-17 years). On average, children were 7 years (*SD*=4.1, range=1.2-16.5) post-treatment. Almost all participants (86%) had at least one abnormal QST parameter compared to age- and sex-matched reference data, however few participants self-reported the presence of sensory abnormalities. Generally, participants exhibited reduced sensitivity across the QST parameters examined (*p*s < .05, *d*s=.40-3.45). A significant minority (45%) also exhibited pain sensitization (p <.001, *d*=.42). Several risk factors for changes in sensory processing were identified, including current age, history of leukemia, certain treatment exposures (e.g., vincristine cumulative dose, major surgery, and bone marrow/stem cell transplant), time off treatment, and higher anxiety and pain catastrophizing scores. Overall, this study demonstrated that somatosensory changes are prevalent in survivors of childhood cancer years after the completion of treatment. Future research is needed to understand long-term implications of altered somatosensation in this complex population.

3.2. Introduction

Therapeutic advancements have improved survival rates for children with cancer (Siegel et al., 2021). However, cancer and its treatment place children at risk for long-term morbidity (S. M. Phillips et al., 2015), including pain (Karlson et al., 2020; Lu et al., 2011), which is often underrecognized and undertreated (Alberts et al., 2018; Stone et al., 2018).

The developing central (CNS) and peripheral (PNS) nervous systems are vulnerable to the effects of cancer and its treatment. Childhood cancers may directly injure the CNS and PNS, and its treatment universally contributes to further tissue damage. Cancer treatments necessitate repeated punctate procedures leading to local tissue damage and prolonged upregulation of nociceptive function (Voscopoulos & Lema, 2010; Weisman et al., 1998). Chemotherapies exert toxic effects that can cause small- and large-fibre dysfunction, neuropathy, and other sequelae (e.g., avascular necrosis) ultimately impacting nervous system functioning and pain (Gilchrist et al., 2017; Kandula et al., 2018; Patel et al., 2008; Taylor et al., 2018). Radiotherapy (Kroczka et al., 2021) and major surgery (Burgoyne et al., 2012; Schreiber et al., 2013) are also associated with long-term nerve injury.

Cancer and its treatment can have lasting consequences on somatosensation. In adult survivors, altered pain and sensory processing, including changes in small- (Aδ, C) and large-fibre (Aβ) function and pain sensitization, have been identified using quantitative sensory testing (QST) (Attal et al., 2009; Boyette-Davis et al., 2013; Dougherty et al., 2007; Martland et al., 2020). Research examining somatosensation in survivors of childhood cancer is scarce. Data specific to this population is needed given

factors unique to the pediatric context. Insults to the nervous system in childhood - a time when developing neural circuits are especially vulnerable to experience (Andrews et al., 2002; Beggs et al., 2012; Walker et al., 2009) - may result in sustained changes to the neurophysiology of sensory and pain perception. QST studies in healthy children have shown that sensitivity changes with age and by sex, with younger children and girls showing more sensitivity (Blankenburg et al., 2011). The vulnerability of childhood is compounded by survivors' risk for anxiety (Schultz et al., 2007) and catastrophic thinking about bodily symptoms (Cunningham et al., 2021; Tutelman et al., 2019). Conceptual models (Alberts et al., 2018; Schulte et al., 2021) of pain after childhood cancer highlight the importance of these psychosocial factors, which modulate affective components of somatosensation (Weisman et al., 1998).

Two QST studies have evaluated sensory processing after childhood cancer; one in survivors of acute lymphoblastic leukemia (ALL) treated with chemotherapy alone (Lieber et al., 2018), and the other in survivors of ALL who received a stem-cell transplant (SCT) (Ruscher et al., 2020). In both studies, three-quarters of participants exhibited signs of large-fibre dysfunction. A greater proportion of children who received a SCT showed signs of small-fibre-dysfunction (88% versus 30%) and pain sensitization (50% versus 30%) compared to those treated with chemotherapy alone (Lieber et al., 2018; Ruscher et al., 2020). Leukemia treatment protocols are notoriously neurotoxic given the type and amount of drugs required, the number of necessary invasive procedures and long duration of treatment (Madhusoodhan et al., 2016). Data on the somatosensory impacts of a broader range of childhood cancers are not available, and further information on risk factors for altered processing is needed.

The primary objective of this study was to quantify generalized differences in pain and sensory processing in survivors of childhood cancer compared to age- and sex-matched reference values using a standardized QST protocol. Survivors of childhood cancer were hypothesized to exhibit altered pain and sensory detection thresholds across the QST parameters. Secondary aims were to examine differences in sensitivity in children with a history of leukemia compared to children with a history of other cancers, and to evaluate the association between demographic, treatment, and psychosocial variables and sensitivity to pain and sensory stimuli.

3.3. Method

3.3.1. Participants

Participants were survivors of childhood cancer (defined as having completed cancer-related treatment) identified from the IWK Heath Centre's pediatric hematology/oncology database and an accompanying parent. The IWK Health Centre is the tertiary care referral center for Maritime Canada representing three provinces and a population base of 1.8 million. Children were eligible to participate if they: (1) were between the ages of 8-17 years, (2) were previously diagnosed with any type of cancer; (3) had completed cancer-related treatment and had not experienced a recurrence or secondary cancer; and (4) were able to speak and understand English. Exclusion criteria included: (1) presence of a medical condition with an associated pain manifestation unrelated to cancer and its effects (e.g., juvenile idiopathic arthritis); (2) parent-reported cognitive difficulties that would impact the child's ability to participate in the study tasks; and (3) hearing or vision impairments not corrected with glasses or hearing aids. Participants and their parents/guardians were initially contacted by letter by a member of

the clinical team to introduce the study. Study staff then followed up by telephone to further explain the study and confirm eligibility.

3.3.2. Procedure

Ethical approval was obtained from the IWK Research Ethics Board (#1023720). Informed written parental consent was obtained for all participants prior to participation. Youth between the ages of 13 and 17 years who were deemed to have capacity to consent according to the procedure published by Nadin and colleagues (Nadin et al., 2018) were asked to provide their consent to participate, while those 8-12 years provided assent. The study conformed to the standards set by the Declaration of Helsinki. The study employed best practices in patient-oriented research, including engagement of patient partners throughout all steps of the research process (Patient-Centered Outcomes Research Institute, 2016).

Participants were recruited between April 2019 and March 2020. Children completed self-report measures (described below) to assess psychosocial functioning and parents completed a demographic questionnaire. Children completed their questionnaires separately from their parents in a testing room with a research assistant. Children then took part in the QST tasks to assess sensory function while parents waited in the research centre lobby. At the end of the study visit, children and parents were debriefed and were each given a $20 gift card as an honorarium. Parents received an additional $15 or $30 gift card based on distance travelled to assist with travel costs.

3.3.3. Measures

Demographic and medical data

Parents reported on their child's age, sex, and race and completed a medication

record detailing their child's current medications and timing of last dose taken. Clinical information including primary diagnosis, age at diagnosis, chemotherapy, radiation, major surgery, bone marrow/stem-cell transplant, and date of final treatment were abstracted from medical records. The Intensity of Treatment Rating Scale 3.0 (ITR-3) was used to classify the overall intensity of treatment received. The ITR-3 is a validated oncology-specific measure that classifies the level of treatment intensity received from 1 (minimally intensive) to 4 (most intensive) based on diagnosis, disease stage, and treatments (Kazak et al., 2012). Ratings were completed by two trained independent raters based on information from participants' medical records, with input from a pediatric oncologist, as needed. No rating discrepancies in ITR-3 ratings occurred.

Pain Catastrophizing

Children reported on their tendency to engage in catastrophic thinking when they are in pain using the Pain Catastrophizing Scale for Children (PCS-C) (Crombez et al., 2003). The PCS-C contains 13 items across three subscales, the tendency to: (1) magnify the threat value, (2) ruminate about, and (3) feel helpless in the face of pain. Each item is rated on a 5-point Likert scale ranging from 0 ("not at all") to 4 ("extremely"). Total scores range from 0-52 with higher scores indicating greater tendency to catastrophize; clinical reference points are low (0–14), moderate (15-25), and high ($\geq$26) catastrophizing (Pielech et al., 2014). Internal consistency in this sample was excellent (α = .92).

Anxiety

Children reported on their anxiety symptoms using the 15-item Total Anxiety subscale of the Revised Children's Anxiety and Depression Scale short version (RCADS-

25) (Ebesutani et al., 2012). Children indicated how often each item applies to them on a 4-point Likert scale ranging from 0 (“never”) to 3 (“always”). Total scores range from 0 to 45 with higher scores indicating more frequent anxiety symptoms. An established cut-off score of ≥ 12 was used to identify participants with clinical symptoms of anxiety (Klaufus et al., 2020). Internal consistency in this sample was good (α = .86).

Self-Report Symptoms of Peripheral Neuropathy

Children reported on symptoms of peripheral neuropathy using the interview items from the pediatric-modified Total Neuropathy Score (Ped-mTNS) (Gilchrist & Tanner, 2013). The questions assess the presence or absence of children’s sensory symptoms (“Do you have any parts of your body that are tingly, numb (can hardly feel) or hurt?”), functional symptoms (“Do you have trouble buttoning shirts or zipping zippers?”, “Do you have trouble walking such as tripping frequently?”, “Do you have trouble going up or down stairs?”), and autonomic symptoms (“Do you feel dizzy or light-headed when you get up out of bed?”, “Do your hands or feet feel hotter or colder than normal?”). If children answer yes to any of the questions, the severity is rated on a 5-point Likert scale ranging from 0 (“none”) to 4 (“symptoms extend above knee or elbow”) for sensory function questions, 0 (“not difficult”) to 4 (“I can’t do that at all”) for functional symptoms questions, and 0 (“Never”) to 4 (“almost always”) for autonomic symptom questions. The highest severity score in each symptom category is recorded as the overall score for Sensory Symptoms, Functional Symptoms and Autonomic Symptoms. Deficits are defined as overall symptom scores >0.

3.3.4. QST

The QST protocol was an abbreviated version of the German Research Network on Neuropathic Pain (DFNS) standardized protocol (Rolke et al., 2006) for children and adolescents (Blankenburg et al., 2010). QST testing was performed in the same quiet room for all participants. Mean room temperature was 22.7°C (*SD*= .92). The QST tests were performed on the thenar eminence of the right hand by a trained female research assistant. The thermal thresholds were established using the method of limits, where the thermal stimulus is gradually increased until the participant reports detection of the sensation (thermal detection thresholds) or the experience of pain (thermal pain thresholds). The mechanical detection and mechanical pain thresholds were determined using a modified method of constant stimuli. In this procedure, mechanical stimuli of ascending intensity are applied, and after each stimulus, participants report whether the stimulus was detected or painful. The threshold is determined when 2/3 applications are detected (mechanical detection threshold) or painful (mechanical pain threshold) (Hirschfeld et al., 2015). Skin surface temperature was measured at the test site immediately prior to beginning the QST protocol using an infrared thermometer (Easy@Home JXB-178, China), the mean of which was 36.2 °C (*SD*=.52). All participants were familiarised with the equipment and instructions prior to the test. Test trials were conducted on areas not tested during the QST session to introduce participants to the procedures. Comprehension of the test instructions was confirmed by having participants repeat the instructions back in their own words. See supplementary materials for a copy of the QST script. All participants wore a blindfold during testing.

Concentration was maintained throughout the protocol, and breaks were provided as needed. Overall, the QST testing protocol took 24.07 minutes (*SD*=3.43) to complete.

Mechanical detection threshold

Mechanical detection thresholds (MDT) were determined using a set of standardized von Frey hairs (North Coast Medical, USA) that exert fixed forces between 0.008g and 300g upon bending. The hairs were applied perpendicularly to the skin, bending for 1 second on a contact area 0.5mm in diameter. Participants were asked to report if they felt the sensation of the hair. If the participant answered "no", then either the same hair or next heaviest hair was randomly chosen to be applied to keep the participant blinded to the algorithm. The hairs were applied in ascending order until the participant responded that they felt the hair. When the participant first reported a sensation, the same filament was applied an additional two times. The threshold was identified when the participant reported feeling the sensation at least two out of three times. The final threshold was the geometric mean of three threshold measures.

Mechanical Pain Threshold

A set of seven weighted pinprick stimulators (MRC Innovative Treatment Solutions) with standardized intensity forces (8, 16, 32, 64, 128, 256, and 512 mN) were used to assess mechanical pain threshold (MPT). Starting with the lowest intensity, Pinpricks were applied perpendicularly to the skin at the centre of the thenar eminence. Participants were asked to reply "sharp" if the stimulus was perceived as sharp, pricking, or stinging. The stimulus was applied an additional two times. The threshold was identified when the participant reported responses were "sharp" at least two out of three times. The final threshold was the geometric mean of the three threshold measures.

Mechanical Pain Sensitivity and Dynamic Mechanical Allodynia

Mechanical pain sensitivity (MPS) was determined using the set of seven weighted pinprick stimulators. Dynamic mechanical allodynia (i.e., DMA; pain to light touch) was determined using a set of three light tactile stimulators: a cotton wisp, a Q-tip fixed to an elastic strip, and a standardized soft brush (Somedic, Sweden). The seven pinpricks and three light tactile stimulators were each applied five times in a pseudorandomized order for a total of 50 stimuli (35 pinprick, 15 tactile). Stimuli were applied with a 10 second interstimulus interval. Participants were asked to give a pain rating using a numerical rating scale ranging from 0 ('no pain') to 10 ('the worst pain you could imagine'). The final MPS was the geometric mean of the 35 pinprick pain ratings. The final DMA was the geometric mean of the 15 pain ratings across the 3 types of light stimuli.

Wind-up Ratio

Wind-up ratio (WUR) was determined by comparing the perceived intensity of a single pinprick (256 mN) applied to a 1cm area on the thenar eminence to the perceived intensity of a series of 10 repetitive stimuli (at a frequency of 1/second) of the same force. Participants were asked to give a pain rating from 0 ('no pain') to 10 ('the worst pain you could imagine') immediately after the first stimulus and again after the series of 10 stimuli. This was done in five repetitions. The WUR was calculated as the ratio between the rating for the single stimulus and the series of stimuli (the mean rating of the five series divided by the mean rating of the five single stimuli). WUR measures the temporal summation of pain (Rolke et al., 2006).

Cool and Warm Detection and Cold and Heat Pain Thresholds

Thermal thresholds were determined using a computer-operated thermal sensory testing device (Neurosensory Analyzer TSA-II, Medoc Inc., Israel). A 30mm x 30mm thermode was attached to the child's thenar eminence using a Velcro strap. The baseline temperature was 32°C and the upper and lower cut-off limits were 0 and 50°C. Thresholds were determined using ramped stimuli at a rate of 1.5°C/second for cool detection (CDT) and warm detection (WDT), and 1.0°C/second for cold pain (CPT) and heat pain (HPT). Participants were asked to identify when they first felt a change in temperature for CDT and WDT and when the sensations first became painful for CPT and HPT by pressing a button. The temperature was automatically recorded once the button was pressed, and the thermode temperature returned to baseline at a rate of 1°C/second for the detection thresholds and 10°C/second for the pain thresholds. CDT and WDT were repeated 4 times, and CPT and HPT were repeated 3 times. The final thresholds were calculated as the arithmetic means of the consecutive trials and expressed as change in degrees from the baseline temperature.

3.3.5. Statistical Analysis

Analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL) and GraphPad Prism 9 (GraphPad Software, Inc, USA) according to standard DFNS procedures for children (Blankenburg et al., 2010).

Data Processing

Absolute QST data are presented as mean ± standard deviation (*SD*). QST parameters (except CPT and HPT) were logarithmically transformed before analysis to achieve a normal distribution. CDT values were multiplied by -1 to allow for log transformation. A negligible constant (+0.1) was added to MPS and DMA pain ratings to

avoid loss of zero-rating values. When log-transformations were performed, the log-scores were used for the calculation of z-scores, *t*-tests, and correlations. For clarity, absolute values representing the original units of each test are reported in tables and used in figures, unless otherwise indicated. $P<0.05$ was considered statistically significant for all tests.

In line with similar QST studies (Edwards et al., 2013; Greenspan et al., 2011) no adjustments were made for multiple comparisons. Past research suggests that such corrections are considered to be overly-conservative in cases where outcome variables are correlated (Pocock, 1983), as is the case among QST parameters (Bhalang et al., 2005). Thus, corrections were not made in the current study.

Calculation of Z-Scores

Log-transformed QST data were standardized using a *z*-transformation based on published age, sex, and site-specific reference values (Blankenburg et al., 2010). The *z*-transformation was calculated using the following formula: $z\text{-score} = (\text{mean}_{\text{participant}} - \text{mean}_{\text{refvalues}}) / SD_{\text{refvalues.}}$

For ease of interpretation of gain and loss of sensitivity and in line with the DFNS protocol (Maier et al., 2010), the sign of the *z*-score was reversed such that scores >0 reflect gain in sensitivity (e.g., lower intensity stimuli required for detection or pain) and scores <0 reflect loss of sensitivity (e.g., higher intensity stimuli required for detection or pain). As such, the *z*-scores for CDT, WDT, HPT, MDT, and MPT were reversed. *Z*-scores outside of the 95% confidence interval of the reference values were considered abnormal, with scores >1.96 indicating gain of somatosensory sensitivity and scores <-

1.96 indicating loss of somatosensory sensitivity. Raw data for DMA are presented and mean values > 0 were considered abnormal (Blankenburg et al., 2010).

Missing Data

For six participants, the WUR could not be calculated because the single pinprick stimulus (the denominator) was rated as "0" across all trials (Rolke et al., 2006). In six additional cases, participants rated the single pinprick stimulus as "0" for only one of the five trials. Here, this value was replaced with the mean value of the other four single pinprick scores and a WUR was calculated (Rolke et al., 2010). Five participants had incomplete WUR data (three participants completed 3/5 trials and two participants completed 2/5 trials). These participants were retained in the analysis by using a last observation carried forward approach for the incomplete trials per published recommendations (Gewandter et al., 2018; Vinik et al., 2016). Missing questionnaire data was minimal (<1%). For questionnaires where at least 80% of items were complete, the individual's mean score was used as a replacement for missing items.

Comparison to Reference Values

Participants' mean (*SD*) *z*-transformed QST data were compared to published age- and sex-matched reference values (Blankenburg et al., 2010) at a mean of "0" and *SD* of "1" with an equal number of cases per parameter using two-sided independent samples *t*-tests according to Magerl and colleagues (Magerl et al., 2010). Thus, total sample sizes for these analysis ranged from N=80 to N=112. Differences in mean threshold values for children with leukemia versus other diagnoses were evaluated using 2-sided *t*-tests for independent samples in line with standard procedures. Effect sizes are reported as

Cohen's *d* and were defined as: *d*=0.2 small; *d*=0.5 medium and *d*=0.8 large (Cohen, 1988).

Examination of Risk Factors

The relationships between sensory thresholds, and clinical and psychological factors were tested using Pearson's correlations. Following the same convention described for the z-scores above, the sign of the correlation was reversed for CDT, WDT, MDT and MPT such that positive correlations represent more sensitivity and negative correlations represent less sensitivity.

Sensitivity Power Analysis

A sensitivity power analysis was performed using G*Power 3.1 (Faul et al., 2007) to determine the minimum detectable effect size (expressed as Cohen's *d*) for differences in QST parameters between the childhood cancer survivor group and the reference values. Given α= 0.05 and β=0.8 for 2-tailed independent t-tests, the lower bound of effect sizes required to achieve significance was of medium size and ranged from *d*=0.47 (for *N*=112) to *d*=0.56 (for *N*=80).

3.4. Results

3.4.1. Study Participants

Of the 156 potential participants who were sent introductory letters, 57 (37%) consented to participate. Reasons for non-participation included: not eligible (*n*=21), unable to reach by telephone (*n*=18), not interested (*n*=42), distance too far (*n*=12), and scheduling conflict (*n*=6). One child declined to complete all QST tasks, opting only to complete the questionnaires. This participant's data was not used in the analysis. The final sample comprised 56 survivors of childhood cancer.

Most participants opted to complete all tests, although 22% of participants declined to participate in the pinprick-related tasks due to fear and anxiety. Overall, 1 participant declined to participate in MPT, 9 declined to participate in MPS, 10 declined to participate in WUR, and 4 declined to participate in DMA. One participant declined to participate in the heat pain task and another was unable to complete the thermal tasks due to equipment failure. The flow of participants through the study is depicted in Figure 1.

3.4.2. Demographic Characteristics and Questionnaires

Children ranged in age from 8 to 17 years (M_{age} = 13.5, *SD* = 3.2) and 48% were female. The three most common cancer diagnoses were acute lymphoblastic leukemia (42.9%), Wilms tumour (12.5%), and neuroblastoma (10.7%). On average, children were diagnosed at 4.9 years of age (*SD*=3.2) and at the time of participation, had been off treatment for 7.1 years (*SD*=4.1). Almost all (92.9%) children identified as White. None of the children had taken any analgesics or adjuvant pain medications 24 hours prior to participation. Almost all children reported that they were right handed (*n*=48, 85.7%), while 10.7% (*n*=6) were left handed and 3.6% (*n*=2) were ambidextrous. See Table 1 for complete demographic characteristics.

Results of the child-reported questionnaires are displayed in Table 2. Sensory deficits were reported in 25.5% of participants, functional deficits in 34.5%, and autonomic deficits in 56.4%, as measured by the Ped-mTNS. Seven participants (12.7%) indicated having parts of their body that hurt: *n*=4 (7.3%) reported pain above the knee or elbow, *n*=2 (3.6%) reported pain extending to the knee or elbow, and *n*=1 (1.8%) reported pain limited to the fingers or toes. While the average level of anxiety in the sample was low, 12 participants (21.4%) exhibited scores above the clinical cut-off. On

average, participants reported moderate levels of pain catastrophizing with 11 participants (19.6%) exhibiting high levels (score $\geq$ 26).

3.4.3. Somatosensory Profile of Survivors of Childhood Cancer

Almost all participants (*n*=48, 85.7%) showed at least one abnormal QST parameter. Of those with abnormalities, *n*=29 (60.4%) had two or more, *n*=11 (22.9%) had three or more, and *n*=7 (14.6%) had four abnormal parameters.

Spectrum of Sensory Abnormalities at the Individual Level

The proportion of participants at the individual level that showed normal, loss, and gain of sensitivity across the QST parameters is shown in Figure 2.

Decreased sensitivity was observed for thermal detection and pain perception in 20 (35.7%) participants overall (CDT: *n*=7, 12.7%; WDT: *n*=1, 1.8%; CPT: *n*=10, 18.2%; HPT: *n*=9, 16.7%). For mechanical detection and pain perception, loss of sensitivity was observed in 26 (46.4%) total participants (MDT: *n*=6, 10.7%; MPT: *n*=24, 43.6%).

Increased sensitivity was observed for thermal pain sensitivity in 2 (3.6%) participants overall, *n*=1 participant each in CPT (1.8%) and HPT (1.8%). A total of 24 (42.9%) participants displayed gain of sensitivity for mechanical sensitivity (MPT: *n*=2, 3.6%; MPS: *n*=21. 44.7%; DMA: *n*=10, 19.2%). Temporal summation, as measured by WUR, was within normative ranges for all participants who completed the parameter (see Table 3 for group means).

Comparison Between Survivors and the Reference Values

As a group, loss of sensitivity was found for all thermal detection and pain perception modalities CDT $t(108) = 5.08$, $p < 0.001$, $d = .97$, WDT $t(108) = 3.21$, $p <$

0.01, *d*=.61, CPT $t(108) = 3.45$, $p < 0.001$, *d*=0.66, HPT $t(106) = 2.07$, $p = .04$, *d*=.40 compared to the reference data. Similarly, loss of sensitivity was found for mechanical detection and pain perception: MDT $t(110) = 2.20$, $p = 0.03$, *d*=0.42, MPT $t(108) = 6.70$, $p < 0.001$, *d*=1.28, and WUR $t(78) = 2.65$, $p = 0.01$, *d*=0.59 compared to the reference data. Gain of sensitivity was limited to MPS $t(92) = 7.60$, $p< 0.001$, *d*=0.42 compared to the reference data (Figure 3).

Comparison Between Survivors with Leukemia versus Other Diagnoses

Participants with a history of leukemia exhibited decreased sensitivity to noxious cold stimuli (i.e., lower CPT) $t(53) = 2.35$, $p < .05$, *d*=.65 and increased sensitivity to noxious mechanical stimuli (i.e., lower MPT) $t(53) = 2.22$, $p < .05$, *d*=.61, compared to children with other cancer diagnoses. Thresholds for the other QST parameters did not vary significantly between groups (Figure 4).

3.4.4. Correlation with Risk Factors

The relationship between key demographic, clinical, and psychosocial factors and the QST parameters are shown in Figure 5. See supplementary material for complete correlation table.

Demographic Correlates

Younger age at the time of study was associated with increased sensitivity to heat pain (HPT: $r = -.32$, $p < .05$), and higher mechanical pain scores (MPS: $r = -.47$, $p <.01$).

Sex was significantly correlated with mechanical detection (MDT: $r = -.30$, $p < .05$), with boys showing less sensitivity than girls (male and female absolute geometric means ± SD: .33 ± .14 vs .63 ± .63).

Similar to the relationship between participant age and sensitivity to heat pain, children who were off treatment for longer showed less sensitivity to heat pain (HPT: r = -.32, p <.05). However, there was no relationship between age at diagnosis and any QST parameters (p's >.05).

Clinical Correlates

Reduced sensitivity to cold pain was associated with having received a greater cumulative dose of vincristine (CPT: r = -.31, p < .05). Conversely, participants with a history of major surgery during treatment exhibited heightened sensitivity to cold pain (CPT: r = .34, p < .05).

Similarly, participants who underwent major surgery had higher thresholds for mechanical pain (MPT: r = .24, p < .05). Participants who received higher cumulative doses of vincristine displayed greater sensitivity (i.e., lower thresholds) to mechanical pain (MPT: r = -.29, p < .05).

Participants who received a bone marrow/stem cell transplant exhibited greater DMA scores compared to those who did not (i.e., allodynia; r = 0.37, p < .01).

Overall intensity of treatment was not associated with any QST parameters, nor was receipt of platinum agents, glucocorticoids, or radiation therapy (p's > .05).

Psychosocial Correlates

Children who scored higher on measures of pain catastrophizing and anxiety displayed increased sensitivity across certain parameters. Specifically, higher pain catastrophizing scores were correlated with increased sensitivity to cold pain (CPT: r = .38, p < .01), and higher anxiety scores were associated with greater sensitivity to mechanical pain (MPT: r = .27, p < .05) and wind up (WUR: r = .41, p <.01).

3.5. Discussion

This study examined the somatosensory profiles of survivors of childhood cancer using a standardized QST protocol. The sensory profiles revealed pervasive changes in somatosensation present years after treatment completion. In this study over 85% of survivors of childhood cancer survivors (mean time off treatment >7 years) had at least one sensory abnormality compared to age and sex-matched reference data.

Generally, participants in this study demonstrated increased thresholds (i.e., reduced sensitivity) across the QST parameters examined. A significant proportion also exhibited pain sensitization, evidenced by gain in sensitivity for MPS and DMA. Examination beyond the group-level data revealed variation across participants in the pattern of sensory abnormalities, with some participants experiencing loss and others experiencing gain of sensitivity across parameters. These findings are in line with past qualitative work suggesting that pain is a changed experience after cancer with some survivors reporting increased pain, others reporting decreased pain, and some reporting no change (Tutelman et al., 2019). The heterogeneity in the somatosensory phenotype is expected given the complexity of diagnoses, painful procedures, treatment exposures, and psychosocial profiles that is inherently characteristic of the cancer experience.

While almost all participants had at least one QST-measured sensory abnormality, only 26% self-reported sensory deficits and only 35% self-reported functional deficits on the Ped-mTNS. It is possible that the sensory differences observed via QST were subclinical and had not progressed to a severity that would cause clinically-significant symptoms to be reported, but may nevertheless confer risk for this later outcome. Alternatively, survivors may have adapted to sensory changes that occurred and therefore

not recognize them as abnormal. Many survivors were treated at an age too young to recall what their sensory processing was like before cancer, thus limiting their ability to identify changes. Baseline sensory testing prior to the initiation of treatment may provide an opportunity for the individualized assessment of sensory changes after childhood cancer. The results of this study may help inform conversations between clinicians and patients about typical expected sensory changes that may occur after treatment.

Chemotherapy-induced peripheral neuropathy (CIPN) is a common neurologic effect of cancer treatment, predominately in survivors of ALL. Sensory abnormalities that accompany the presentation of CIPN can include negative (e.g., hypoesthesia) and/or positive (e.g., hyperalgesia) signs (Paice et al., 2017), and both were observed in this study. While a diagnosis of CIPN cannot be made based on QST alone, hypoesthesia were present in 13% of participants for thermal and 10% for mechanical stimuli, which may reflect the deafferentation of small- and large-fibres secondary to neurotoxic treatments. Pain sensitization was observed in 45% of participants. This value is likely an underestimation given that 22% of participants declined to participate in pinprick tasks. Nonetheless, the high level of sensitization observed links with existing research and may be due to both peripheral and central mechanisms.

Peripherally, mechanical hypersensitivity to pinprick and light touch may reflect the hyperexcitability of peripheral neurons due to neural damage caused by chemotherapy and repeated exposure to noxious stimuli during treatment. Vincristine is believed to cause peripheral hyperexcitability, secondary to distal axonopathy (i.e., nerve degeneration beginning at the terminal of peripheral fibres) and Wallerian degeneration (i.e., self-destructive retrograde degeneration of an axon resulting from a nerve lesion)

(Zajączkowska et al., 2019). In this study, participants with a history of leukemia displayed greater sensitivity to noxious mechanical stimuli (e.g., lower MPT). Children with leukemia received significantly greater cumulative doses of vincristine compared to children with other diagnoses (Table 1), which was associated with increased sensitivity to mechanical pain (Figure 5). This finding is in line with translational work which has found mechanical pain hypersensitivity in animal models exposed to vincristine (Schappacher et al., 2017), and clinical studies with vincristine-treated adult cancer survivors (Dougherty et al., 2007).

Existing literature suggests that 30-52% of survivors of pediatric ALL experience pain sensitization measured by QST (Lieber et al., 2018; Ruscher et al., 2020). However, these studies were conducted in samples comprised exclusively of survivors of ALL and were unable to examine the potential impact of vincristine on sensory outcomes nor the differences between children with leukemia versus other diagnoses. The current study builds on this existing work and lends support to the hypothesis that survivors of childhood leukemia may be a high-risk group for somatosensory changes after cancer, perhaps due to the type (e.g., vincristine) and amount (e.g., cumulative dose) of neurotoxic treatments received. That said, cumulative dose of vincristine has been inconsistently related to neurotoxicity (Kandula et al., 2016; E. M. L. Smith et al., 2020) and requires further examination. Children with hematologic malignancies also receive other drugs with known neurotoxic effects, including those administered intrathecally (Kwong et al., 2009; Ness et al., 2012), and also undergo repeated invasive procedures (e.g., lumbar punctures) over many years of treatment. It is possible that these factors cumulatively and uniquely prime children with a history of leukemia to sensory changes.

Nevertheless, somatosensation is a complex biopsychosocial process, particularly in the context of cancer survivorship. In line with proposed conceptual models (Alberts et al., 2018; Schulte et al., 2021), it is likely that a range of factors beyond those that are treatment-related (e.g., sleep, physical activity, other late effects of treatment) contribute to pain and sensory processing in this population.

Pain sensitization may also reflect the involvement of central mechanisms. Hyperactivity in injured peripheral nerves can lead to the sensitization of central nociceptive pathways via synaptic facilitation in the dorsal horn (Meacham et al., 2017). Central sensitization is believed to be a key mechanism underpinning the development and maintenance of chronic pain (Harte et al., 2018). Chronic pain in survivors of childhood cancer is increasingly recognized as a potential late effect of cancer treatment (Alberts et al., 2018; Schulte et al., 2021). While only 13% of participants in this study reported having pain on the Ped-mTNS, as many as 45% exhibited pain sensitization on QST. These results may reflect early sensory changes that precede future chronic pain pathology. That said, overall reduced sensory sensitivity has also been hypothesized as a risk factor for the development of persistent widespread pain (Moseley & Vlaeyen, 2015). Prospective longitudinal studies would be valuable to elucidate the trajectory of symptoms over time and their relationship with QST parameters.

In this study, several demographic, clinical, and psychosocial variables were associated with somatosensation in survivors of childhood cancer. The overall treatment intensity was not correlated with any QST parameters. However, the relationships of QST parameters identified with intrathecal chemotherapy, history of major surgery, and higher cumulative dose of vincristine suggest that specific examination of cumulative neurotoxic

risk may be more informative as opposed to a global rating of treatment intensity. Children who received a bone marrow/stem-cell transplant displayed higher DMA scores. This finding builds on data from Ruscher and colleagues (Ruscher et al., 2020), highlighting this subgroup as potentially high risk for sensitization.

Interestingly, albeit not unexpectedly, children with greater self-reported pain catastrophizing and anxiety displayed increased sensitivity across different parameters. Similar findings have been noted in adult cancer survivors (Edwards et al., 2013) and children with other chronic illnesses such as sickle cell disease (Bakshi et al., 2017) and arthritis (Cornelissen et al., 2014). Anxiety and catastrophizing are known to modulate pain sensitivity in healthy children (Birnie, Chambers, et al., 2017; Boerner et al., 2016; Verhoeven et al., 2012), through supraspinal mechanisms (e.g., attention, memory, coping) (Edwards et al., 2011). Anxiety sensitivity is another key construct underpinning the sensory experience (Tsao et al., 2006) which should be examined in future studies.

The relationship between emotional processing and pain sensitivity may be particularly relevant for survivors of childhood cancer. Children with cancer often receive inadequate analgesia for painful procedures (Plummer et al., 2017), which can lead to a cycle of increased distress and pain in future procedures (Chen et al., 2000; Weisman et al., 1998). This study demonstrates that the relationship between pain catastrophizing, anxiety and increased pain sensitivity persists in long term survivors, and underscores the necessity of adequately managing pain during treatment and into survivorship. A significant proportion of survivors may continue to experience significant anxiety and distress about needle procedures, which has implications for the lifelong follow-up care required after childhood cancer.

This study had many strengths including the inclusion of survivors of various forms of childhood cancer, use of a standardized QST protocol, and the comprehensive examination of risk factors. There are some limitations to be acknowledged. While a standardized QST protocol for children was used, there may be contextual differences between the data in this study and reference data collected at a different laboratory. Further, multiple modalities were evaluated using a comprehensive QST protocol but did not include vibration nor pressure pain, which may yield important insights into function of deeper nociceptors. Additionally, QST was performed at one body site to allow for optimal comparison to reference values, and results may differ when examined at other sites across the body. Finally, while the diverse sample of childhood cancer survivors in this study allowed us to overcome the limitations of past research only examining survivors of ALL, the current sample was quite heterogeneous with regards to clinical variables which may limit the generalizability of the findings. Conversely, race was relatively homogeneous. Future multisite studies with more demographically diverse and larger numbers of subjects and longitudinal data collected post-treatment will be important in leading to prevention and intervention measures related to pain in this population.

In conclusion, this study demonstrated that somatosensory abnormalities are prevalent in survivors of childhood cancer years after the completion of treatment. These findings may guide clinical conversations about pain and sensory changes after cancer, and add to the growing body of literature pointing to the need for personalized approaches for survivorship care (Mayer & Alfano, 2019). Future research is needed to understand long-term implications of altered somatosensation in this complex population.

3.6. Acknowledgements

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3.7. Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

3.8. References

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3.9. Figures

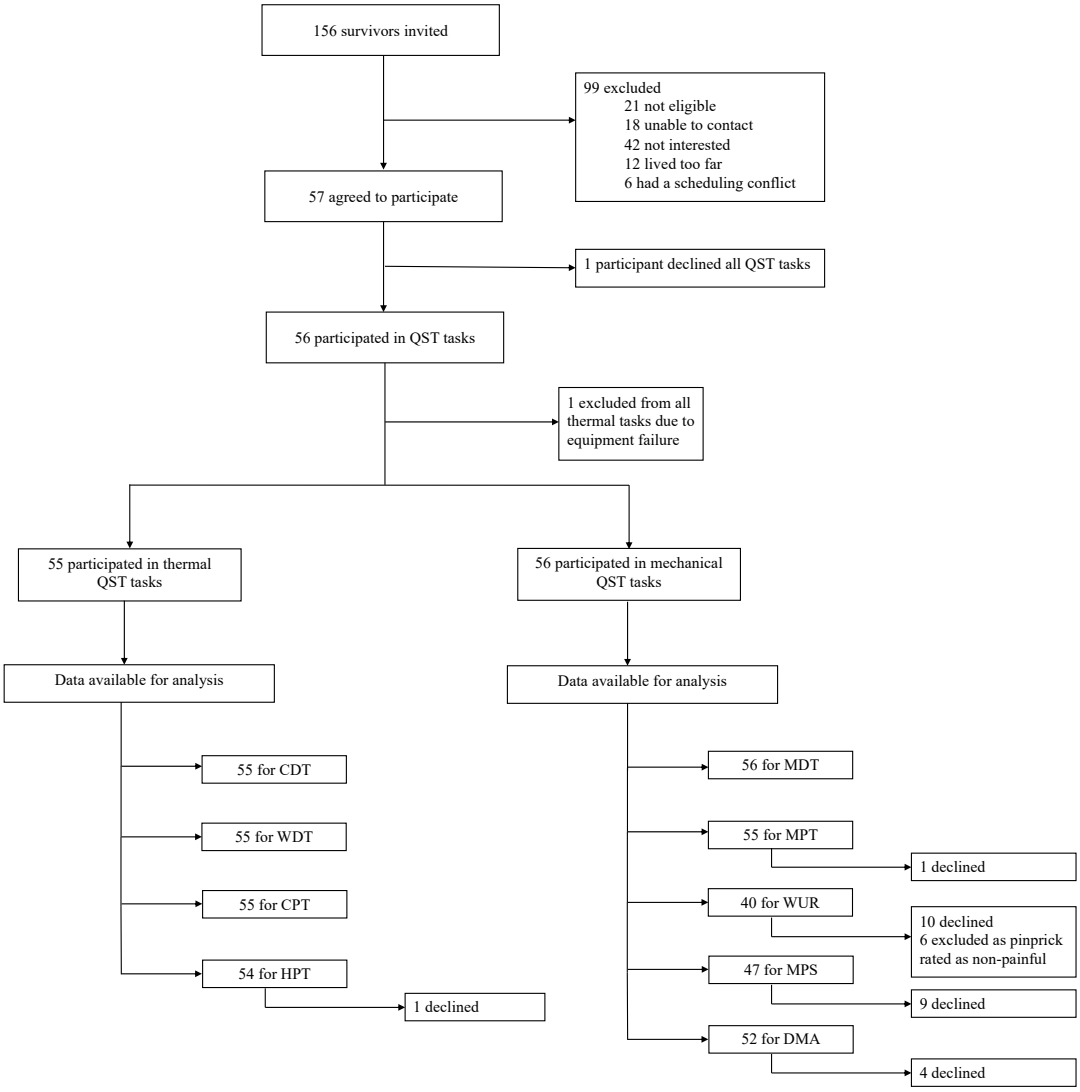

Figure 3.1. Flow of participants through the study.

QST, quantitative sensory testing; CDT, cold detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind up ratio. DMA, dynamic mechanical allodynia.

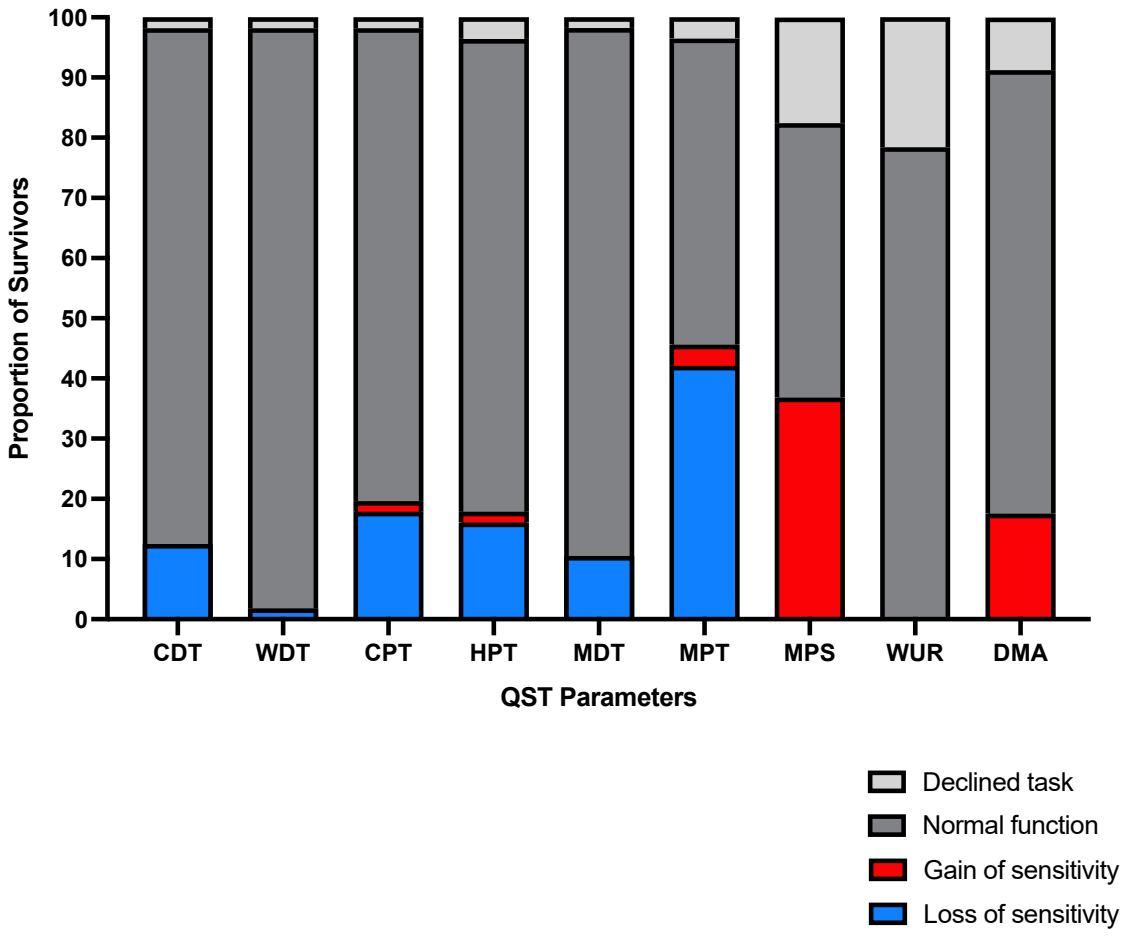

Figure 3.2. Patterns of sensory abnormalities in childhood cancer survivors.

The proportion of individual z-scores above the upper bound of the 95% CI of the reference data (i.e., > 1.96) are represented in red and the proportion of individual z-scores below the lower bound of the 95% CI of the reference data (i.e., <-1.96) are represented in blue. The proportion of children who declined to complete each task is shown in light grey. CDT, cold detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind up ratio. DMA, dynamic mechanical allodynia.

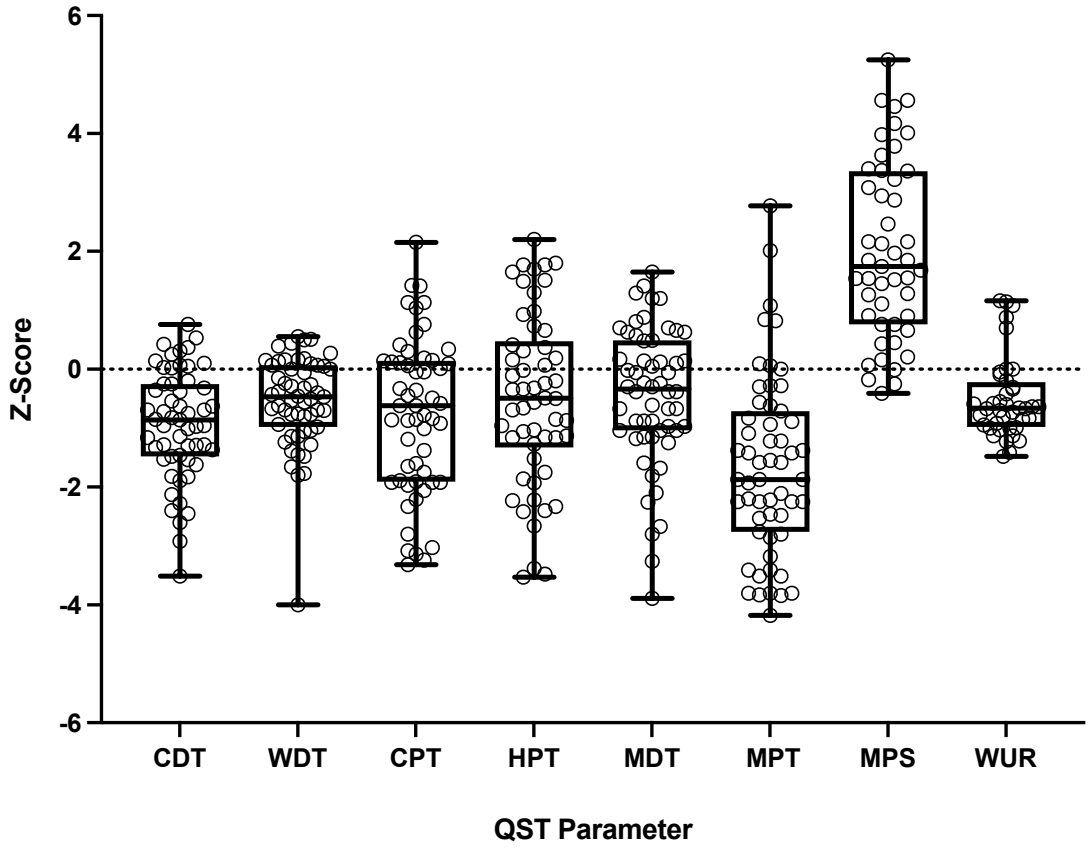

Figure 3.3. Quantitative sensory testing results in childhood cancer survivors.

Data for the QST parameters are presented as z-scores. Single dots represent individuals' mean scores. Box and Whisker plot illustrates the group median, IQR and range. Z-scores outside of the 95% confidence interval of the reference data were considered abnormal, with scores >1.96 indicating gain of sensitivity and scores <-1.96 indicating loss of sensitivity. QST, quantitative sensory testing; CDT, cold detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind up ratio. Dynamic mechanical allodynia is not presented as z-scores cannot be calculated for this parameter.

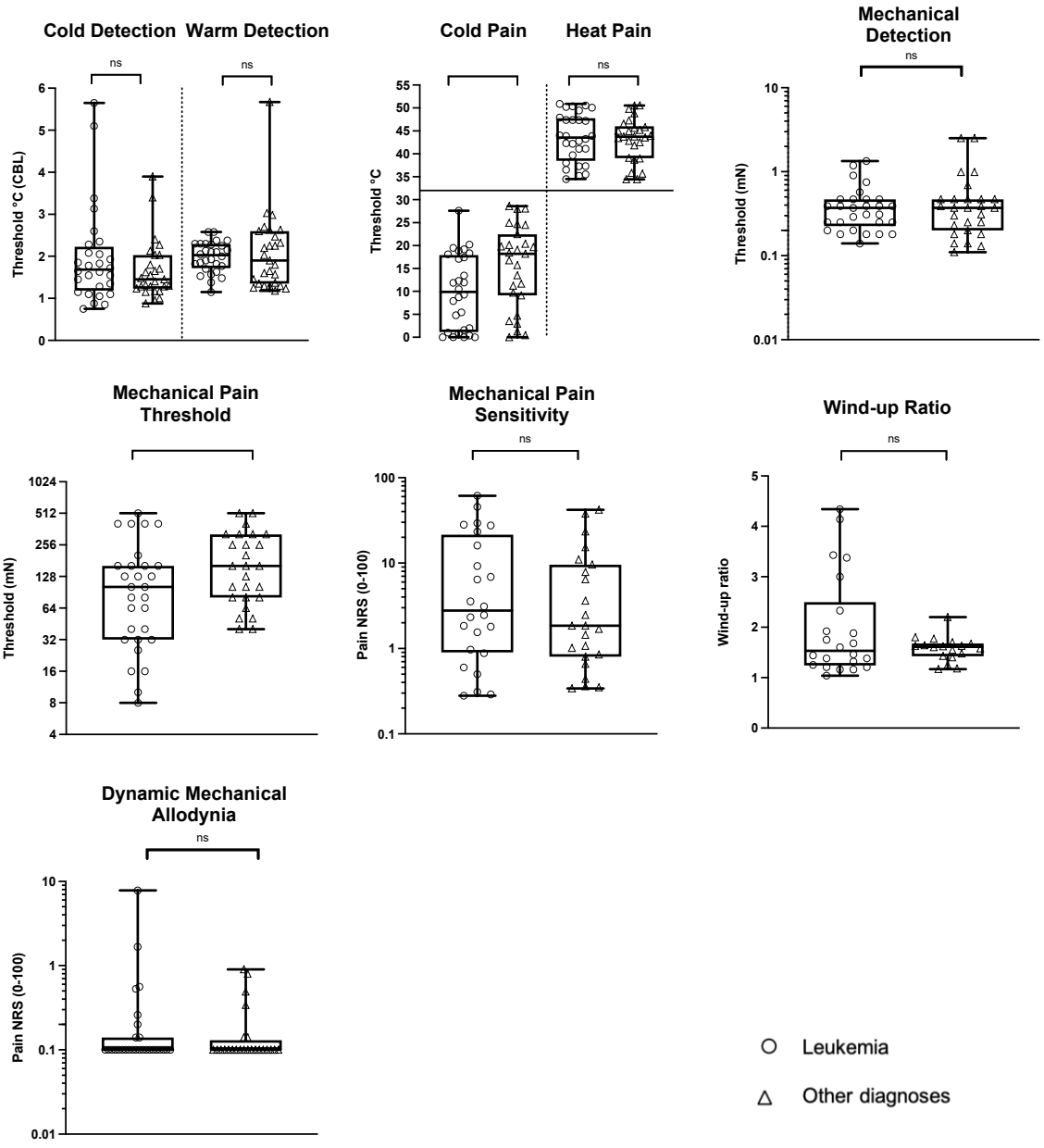

Figure 3.4. Comparison of somatosensory profiles between children with histories of leukemia (circles; *n* = 29) versus other diagnoses (triangles; *n* = 27).

Children with a history of leukemia had less sensitivity to cold pain and greater sensitivity to mechanical pain. Single dots represent individuals' mean scores on each parameter. Box and Whisker plots illustrate the group median, IQR and range. CBL, change from baseline; mN, millinewtons; NRS, numerical rating scale. *p<0.05.

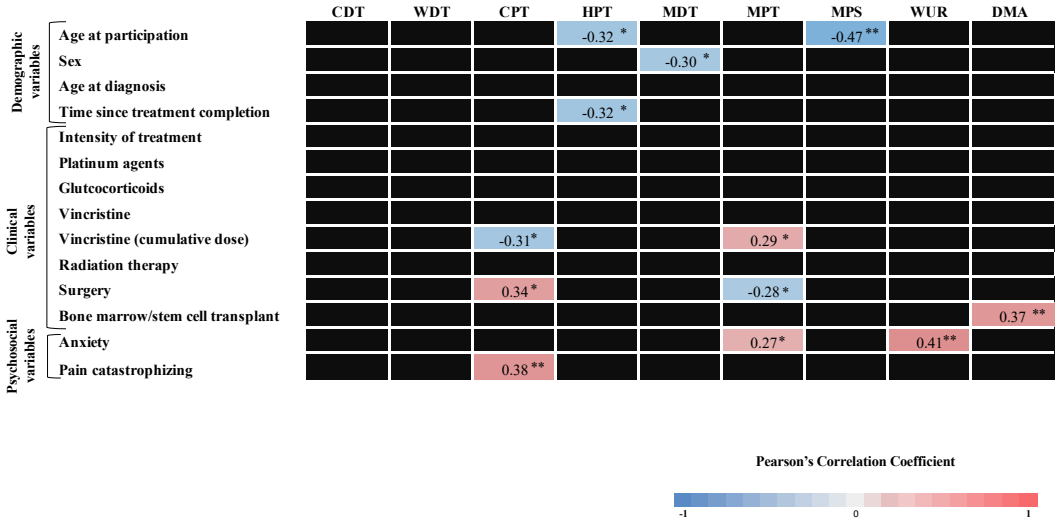

Figure 3.5. Relationship between demographic, clinical, and psychosocial variables and QST parameters in survivors of childhood cancer.

Heat map depicts Pearson's correlation coefficients. Significant correlations are colored red (positive relationship) or blue (negative relationship). See supplementary material for complete correlation table. CDT, cold detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind up ratio. * $p < 0.05$; ** $p < 0.01$.

3.10. Tables

Table 3.1. Demographic Characteristic

Characteristics	Total (*N*=56)	Leukemia (*N*=29)	Other Diagnosis (*N*=27)	*p*-value*
Age at participation, mean (*SD*) range, y	13.5 (3.2) 8.4-17.9	13.5 (3.1) 8.5-17.8	13.5 (3.3) 8.4-17.9	0.99
Sex, no. female (%)	27 (48.2)	15 (51.7)	12 (44.4)	0.61
Age at diagnosis, mean (*SD*) range, y	4.9 (3.2) 0.2-13.8	5.0 (2.9) 0.3-11.3	4.9 (3.6) 0.2-13.8	0.89
Time since treatment completion, mean (*SD*) range, y	7.1 (4.1) 1.2-16.5	6.3 (3.5) 1.3-14.5	7.9 (4.6) 1.2-16.5	0.12
Race no. (%)				0.80
White	52 (92.9)	27 (93.1)	25 (92.6)	
Native/Aboriginal	3 (5.4)	2 (6.9)	1 (3.7)	
Other	1 (1.8)	0 (0)	1 (3.7)	
Diagnosis, no. (%)				
Leukemia	29 (51.8)	29 (100)	0 (0)	
Wilms Tumor	7 (12.5)	0 (0)	7 (12.5)	
Lymphoma	5 (8.9)	0 (0)	5 (8.9)	
Sarcoma	5 (8.9)	0 (0)	5 (8.9)	
CNS Tumor	2 (3.6)	0 (0)	2 (3.6)	
Other†	2 (3.6)	0 (0)	2 (3.6)	
Chemotherapy, no. (%)	55 (98.2)	29 (100)	26 (96.3)	0.48
Platinum agents	11 (19.6)	1 (3.4)	10 (37)	<0.01
Glucocorticoids	31 (56.4)	24 (82.8)	7 (25.9)	<0.001
Vincristine	47 (83.9)	24 (82.8)	23 (85.2)	0.71
Cumulative dose, mean (*SD*), range, mg/m^2	38.5 (25.3) 2.0-79.5	59.5 (15.1) 22.5-79.5	16.5 (11.0) 2.0-45	<0.001
Radiation, no. (%)	15 (26.8)	4 (13.8)	11 (40.7)	<0.05
CNS-directed	4 (7.1)	3 (10.3)	1 (3.7)	<0.05
Surgery, no. (%)	27 (48.2)	1 (3.4)	26 (96.3)	<0.001
Resection (tumor or organ)	22 (39.3)	0 (0)	22 (81.5)	<0.001

Open Biopsy	14 (25)	1 (3.4)	13 (48.1)	<0.001
Other ‡	4 (7.1)	0 (0)	4 (14.8)	<0.001
Bone marrow / stem cell transplant, no. (%)	8 (14.3)	2 (6.9)	6 (22.2)	0.14
Intensity of Treatment, mean (*SD*) range	2.7 (.90) 1-4	2.8 (0.7) 2-4	2.6 (1.0) 1-4	0.50

Note. CNS = central nervous system. *Independent samples t-test or Fisher's exact text. † Other diagnoses included the following: retinoblastoma and hepatoblastoma. ‡ Other surgeries included the following: enucleation, solid organ transplant, thoracotomy, and vaginoplasty.

Table 3.2. Self-Report Measures

	Total (N=56)		Leukemia (N=29)		Other Diagnosis (N=27)	
	Mean (SD), range	% with deficit	Mean (SD), range	% with deficit	Mean (SD), range	% with deficit
Ped-mTNS items						
Sensory Symptoms	0.67 (1.35), 0-4	25.5	0.69 (1.31), 0-4	31.0	0.68 (1.44), 0-4	20
Functional Symptoms	0.56 (0.92), 0-4	34.5	0.55 (0.95), 0-4	34.5	0.48 (0.77), 0-2	32
Autonomic Symptoms	1.22 (1.26), 0-4	56.4	1.07 (1.36), 0-4	44.8	1.36 (1.15), 0-3	68
Anxiety Symptoms	9.32 (7.14), 0-30		8.55 (5.95), 0-29		9.59 (7.89), 1-30	
Pain Catastrophizing	15.07 (10.40), 0-43		15.36 (11.22), 0-43		14.26 (9.47), 3-39	

Note. Ped-mTNS = pediatric-modified Total Neuropathy Score; deficit refers to a score >0 on the ped-mTNS.

Table 3.3. QST Absolute Values for Childhood Cancer Survivors

QST Parameter	Units	n	Mean	SD	95% CI	
					low	high
Cold detection threshold (CDT)	Δ °C	55	1.82	.96	1.55	2.01
Warm detection threshold (WDT)	Δ °C	55	2.03	.70	1.84	2.21
Cold pain threshold (CPT)	°C	55	12.65	8.92	10.24	15.06
Heat pain threshold (HPT)	°C	54	43.33	5.0	41.97	44.69
Mechanical detection threshold (MDT)	mN	56	0.47	0.47	0.35	0.60
Mechanical pain threshold (MPT)	mN	55	167.50	144.34	128.45	206.49
Mechanical pain sensitivity (MPS)	NRS	47	9.52	14.29	5.33	13.71
Wind-up-ratio (WUR)	ratio	40	1.79	0.79	1.54	2.04
Dynamic mechanical allodynia (DMA)	NRS	52	0.34	1.09	0.04	0.65

Note. C = Celsius; mN = millinewtons; NRS = numerical rating scale.

3.11. Supplementary Materials

Supplementary Materials – Appendix A

QST Script

Instructions for performing QST in children and adolescents (adapted from Blankenberg et al., 2010 and Cornelissen et al., 2014).

General Instructions

In the following tests, we will explore, using various procedures, how you perceive temperature changes as well as touch stimuli. In addition, we will examine the point at which different test stimuli are perceived as painful. If you have not understood the test instructions, please feel free to immediately ask for clarification.

Mechanical Detection Threshold

This is a test of your ability to detect light touch. I will press these nylon hairs to the skin on your hand. Please tell me if you feel it or not"

Mechanical Pain Threshold

This is a test of your ability to detect a 'sharp' sensation. I will gently touch your hand with the Pinpricks. If you feel the Pinprick touching your skin without any pricking or stinging, say 'blunt'. Please say 'sharp' immediately if it feels like a 'sharp', 'pricking' or 'stinging' sensation.

Mechanical Pain Sensitivity and Dynamic Mechanical Allodynia

I will touch your hand with the Pinpricks and gently moving stimuli. After each stimuli, give me a number between 0-10 for how much it hurt where 0 means 'no pain' and 10 means the 'worst pain you could imagine'.

Wind-Up Ratio

Participants will be given the following instructions before receiving a single Pinprick: *I will now touch your hand with a single Pinprick. After, give me a number between 0-10 for how much it hurt where 0 means 'no pain' and 10 means the 'worst pain you could imagine.'*

Once the participant has rated the single pinprick stimulus, the following instructions will be given: *I will now touch your hand using the Pinprick 10 times in a row. After*, *give me a number between 0-10 for how much it hurt where 0 means 'no pain' and 10 means the 'worst pain you could imagine'. We will then repeat this two more times.*

Thermal Tasks

The device placed on your skin is able to both warm and cool the skin. In addition, you have been given a stop button that enables you to immediately stop the ongoing test stimulus at any time. For every test, I will explain to you when to use the stop button."

Cool Detection Threshold

Please press the stop button at the point where you start to feel the change in temperature. This procedure will be performed a total of four times." Once pressed, the participant will be asked, *"What did you feel?"* Instructions are repeated before each trial once the thermode has returned to baseline temperature.

Warm Detection Threshold

Please press the stop button at the point where you start to feel the change in temperature. This procedure will be performed a total of four times." Once pressed, the participant will be asked, *"What did you feel?"* Instructions are repeated before each trial once the thermode has returned to baseline temperature.

Cold Pain Threshold

The temperature of the skin will go down from 'cool' to 'cold'. Please press the stop button immediately as soon as it feels so cold you don't want it on your skin anymore, like holding ice or a Popsicle.

Heat Pain Threshold

The temperature of the skin will go from 'warm' to 'hot'. Please press the stop button as soon as the temperature feels so hot you don't want it on your skin anymore, like holding a cup of hot coffee or hot chocolate.

Supplementary Materials – Appendix B

Correlations among demographic, clinical and psychosocial variables and QST parameters in survivors of childhood cancer

Variable	CDT	WDT	CPT	HPT	MDT	MPT	MPS	WUR	DMA
Age at participation	0.01	0.00	-0.07	-0.32*	-0.07	-0.21	-0.47**	0.28	0.05
Sex	0.21	0.11	-0.10	-0.17	-0.30*	0.03	0.00	0.08	-0.13
Age at diagnosis	0.21	0.25	-0.04	0.11	0.07	-0.05	-0.15	-0.10	0.09
Time since treatment completion	-0.15	-0.21	0.04	-0.32*	-0.11	-0.21	-0.22	0.26	0.00
Intensity of treatment	0.07	0.12	-0.05	0.00	-0.03	0.19	0.16	0.06	0.22
Platinum agents	0.11	0.11	-0.01	-0.17	-0.12	-0.15	-0.04	-0.16	-0.06
Glucocorticoids	0.10	0.01	-0.21	0.11	0.03	0.02	0.05	-0.12	0.11
Vincristine	-0.02	-0.01	0.05	0.14	0.03	-0.03	0.18	-0.23	0.08
Vincristine (cumulative dose)	-0.01	0.06	-0.31*	-0.02	0.09	0.29*	0.09	0.08	-0.09
Radiation therapy	-0.06	0.00	0.12	0.09	0.14	-0.06	0.08	-0.18	0.27
Surgery	0.11	-0.03	0.34*	0.08	-0.03	-0.28*	-0.13	-0.26	-0.12
Bone marrow/stem cell transplant	-0.03	0.00	-0.07	-0.15	-0.15	0.04	0.18	-0.12	0.37**
Anxiety	0.06	0.01	0.06	-0.11	-0.03	0.27*	-0.10	0.41**	-0.09
Pain catastrophizing	0.01	0.09	0.38**	0.12	-0.11	0.02	-0.07	0.24	-0.14

Note. CDT, cold detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind up ratio. * $p < 0.05$; ** $p < 0.01$.

CHAPTER 4: MEASURING FEAR OF CANCER RECURRENCE IN SURVIVORS OF CHILDHOOD CANCER: DEVELOPMENT AND PRELIINARY VALIDATION OF THE FCRI-CHILD AND FCRI-PARENT VERSIONS

The manuscript prepared for this study is presented below. Perri Tutelman, under the supervision of Dr. Christine Chambers, was responsible for developing the research question, methodology and analytic approach, and obtaining ethical approval and funding. She developed the study protocol and data collection procedures, contributed substantially to data collection, and oversaw staff and volunteers who contributed to these activities. Of note, because the data analyzed in this manuscript were pooled from the IWK Health Centre and two other sources (the University of Calgary and Stanford University), the co-author leads from these two other sites led the ethics submissions and data collection procedures there. Ms. Tutelman was the lead on data analysis and interpretation, with the support of her co-authors, and wrote the initial draft of the manuscript. Prior to submission, she received and incorporated feedback from the study's co-authors. The manuscript was submitted to *Psycho-Oncology* on July 15, 2021 and reviews were received on August 17, 2021. The current reference for this manuscript is:

Tutelman, P.R, Chambers, C.T, Heathcote, L.C, Fernandez, C.V, Flanders, A., Patton, M., Schulte, F.S.M., Guilcher, G.M.T., Simard, S., MacLeod, J., & Stern, M. (under review). Measuring Fear of Cancer Recurrence in Survivors of Childhood Cancer: Development and Preliminary Validation of the FCRI-Child and FCRI-Parent Versions. *Psycho-Oncology.*

4.1. Abstract

Objective: Fear of cancer recurrence (FCR) is a significant unmet need for cancer survivors. However, there are no validated FCR measures for child survivors. The objectives of this study were to adapt the Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF) for survivors of childhood cancer aged 8-18 years (FCRI-C) and their parents (FCRI-P) and to examine their initial psychometric properties.

Methods: The wording of the FCRI-SF was adapted through expert panel input and cognitive interviews. The factor structure, internal consistency and construct and criterion validity of the FCRI-C and FCRI-P were examined in 124 survivors of childhood cancer (43% female; M_{age}= 14.58 years, *SD*=2.90, range=8-18 years) and 106 parents (90% mothers).

Results: All FCRI-SF items were retained for the FCRI-C with simplified language. The internal consistencies of the FCRI-C (α= .88) and FCRI-P (α= .83) were good. A one-factor structure was a good fit to the data for both measures. Higher scores on the FCRI-C and FCRI-P were associated with greater intolerance of uncertainty and pain catastrophizing for children and parents. Children with higher FCR also reported more hypervigilance to bodily symptoms. Higher parent FCR was related to greater child healthcare utilization. Children reported significantly lower levels of FCR compared to parents.

Conclusions: The FCRI-C and FCRI-P demonstrated strong reliability and validity. This study offers preliminary data to support the use of the FCRI-C and FCRI-P to measure FCR in survivors of childhood cancer aged 8-18 years and their parents.

4.2. Introduction

Defined as, "the fear, worry, or concern about cancer returning or progressing" (Lebel, Ozakinci, et al., 2016), fear of cancer recurrence (FCR) is a significant psychosocial concern for adult cancer survivors and their caregivers (Simard et al., 2013). At clinical levels, FCR is associated with psychological distress, hypervigilance to bodily symptoms, and greater healthcare utilization, including increased outpatient and emergency visits (Champagne et al., 2018; Lebel et al., 2013; Simard et al., 2013). While FCR research to date has focused on adult (>18 years) survivors, there is growing evidence that FCR may also be a concern for survivors of childhood cancer and their parents (Tutelman et al., 2019; Wakefield et al., 2011; Wroot et al., 2020). However, examination of this construct in the pediatric population has been hampered by the lack of a validated pediatric measure.

To date, three quantitative studies have included child survivors (<18 years) in self-report studies examining FCR. Wroot and colleagues (Wroot et al., 2020) reported that 43% of survivors of childhood cancer (aged 8-21 years) attending a pediatric survivorship clinic endorsed an item about FCR. In another study using a single FCR item found that FCR was positively linked with symptoms of post-traumatic stress and post-traumatic growth in survivors aged 11-27 years (Koutná et al., 2021). A third study found that FCR, as measured by the adult-validated Cancer Worry Scale, was related to worry about somatic symptoms in survivors aged 8-25 years (Cunningham et al., 2021). While these studies provide key initial data suggesting that FCR is salient for survivors of childhood cancer, they are limited by their use of single items and measures not validated for use with children. A psychometrically-sound instrument that measures FCR in

pediatric (<18 years) populations is needed to understand the experience of FCR in younger survivors and lay the groundwork for future observational and intervention research.

The Fear of Cancer Recurrence Inventory (FCRI) is the most common and psychometrically strong self-report measure of FCR in adult survivors (Thewes et al., 2012). The FCRI was initially developed as a 42-item questionnaire to assess FCR as a multidimensional construct (Lebel, Simard, et al., 2016; Simard & Savard, 2009). Recently, the 9-item severity subscale - which measures the intensity of FCR and is most directly related to the level of fear - has been adopted as a short form (FCRI-SF) (Simard & Savard, 2015). The FCRI-SF has good internal consistency, adequate test-retest reliability, and moderate-to-strong correlations with measures of convergent and construct validity in adult survivors (Simard & Savard, 2015). It has been translated into multiple languages and is widely used in research and clinical practice (A. B. Smith et al., 2020). Various FCRI-SF cut-off scores for clinical FCR have been proposed (e.g., scores $\geq$ 13 (Simard & Savard, 2015), $\geq$ 16 (Simard & Savard, 2015), or $\geq$ 22 (Fardell et al., 2018)), with 30.0% to 53.9% of adult survivors meeting or exceeding them (A. B. Smith et al., 2020). Caregivers report FCR at even higher levels that survivors themselves (Hodges & Humphris, 2009; Simard et al., 2013). Parents of child survivors could be particularly affected (Tutelman et al., 2019), but this has yet to be examined quantitatively. The widespread use of the FCRI-SF and its robust psychometric profile make it an ideal candidate to adapt for use with children and their parents. However, the current wording is complex and would require simplification to be readily understood by children. A child-adapted version of the FCRI-SF would allow for direct comparisons of

FCR between pediatric and adult survivor populations, facilitating crucial developmental research and clinical application.

The objectives of the current study were to: (1) adapt the FCRI-SF into a measure for children aged 8-18 years (the Fear of Cancer Recurrence Inventory – Child Version (FCRI-C)) and their parents (the Fear of Cancer Recurrence Inventory – Parent Version (FCRI-P)); (2) examine the preliminary psychometric properties of the FCRI-C and FCRI-P; and (3) examine the relationship between the FCRI-C, FCRI-P and child demographic characteristics and measures of construct and criterion validity.

4.3. Method

4.3.1. Participants and Procedures

Participants were survivors of childhood cancer and parents of survivors recruited at one of three North American children's hospitals. To be included survivors had to: (1) be between the ages of 8-18 years at the time of participation; (2) have a history of cancer; (3) have completed cancer-related treatment; and (3) read and understand English. Parents had to have a child meeting the above criteria and be able to read and understand English. All children and parents provided written informed consent or assent prior to participation. Data collection was approved by the ethics committees at all sites (IWK Health Centre: #1023720, Alberta Children's Hospital: #HREBA.CC-17-0059, and Stanford University School of Medicine: #44463).

The sample comprised 124 children and 106 parents. Of the children and parents participating, 99 were dyads. On average, children were 14.58 (*SD*=2.9) years old at the time of participation (age range = 8.42-18.00 years). Children had a mean age of 7.06 (*SD*=4.6) years at diagnosis and had been off treatment for an average of 6.32 (*SD* = 4.1)

years. Approximately half (50.8%) of survivors had a history of leukemia. Almost all parents were mothers (90.1%). See Table S1 for further demographic information.

4.3.2. Measure Development: The FCRI-C and FCRI-P

The Fear of Cancer Recurrence Inventory – Child version (FCRI-C)

The FCRI-C was adapted from the original version of the FCRI-SF (Simard & Savard, 2015). The FCRI-SF is a 9-item self-report measure that comprised of a single factor and assesses the severity of FCR. The FCRI-SF evaluates the presence, frequency, intensity, and duration of thoughts about FCR, in addition to an individual's perceived risk of recurrence. Items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("a great deal"). One item (#5) is reverse scored before items are summed to create a total score (range=0-36). Following the procedures used in past research to adapt adult measures for children (Wright & Asmundson, 2003), the FCRI-SF was modified through a process of expert panel input and cognitive interviews with survivors of childhood cancer.

Item Adaptation

The FCRI-SF was initially adapted for children based on feedback from an expert panel. The panel comprised eight experts including pediatric oncologists (*n*=2), child life specialists (*n*=2), a pediatric psychologist (*n*=1), a pediatric oncology survivorship nurse (*n*=1), and young adult survivors of childhood cancer (*n*=2). The panel reviewed the FCRI-SF and provided recommendations regarding wording simplification. The developer of the original FCRI-SF (SS) also provided input to maintain the integrity of the scale. All 9 items and the existing Likert scale were retained from the FCRI-SF for the FCRI-C to maximize comparability with the adult measure. Throughout, the phrase

"*the possibility of cancer recurrence*" was changed to "*the possibility of having cancer again*". The wording of the individual questions was also simplified. For instance, *'When I think about the possibility of cancer recurrence, this triggers other unpleasant thoughts or images (such as death, suffering, the consequences for my family)'* (item 4) was simplified to, '*When I think about the possibility of having cancer again, I think about other bad things that could happen (like dying, or the impact on my family)'.*

Cognitive Interviews.

Cognitive interviews were conducted by the first author (PRT) with three survivors of childhood cancer to evaluate children's comprehension of the initial FCRI-C items. Two were between ages 8-10 years, and one was between 15-17 years. Cognitive interviewing was performed according to the four step procedure described by Bowen and colleagues (Bowen et al., 2004). The children demonstrated excellent comprehension of the initial FCRI-C items, recall periods, and response options. Minor wording changes were made to enhance understandability (e.g., participants expressed difficulty understanding the meaning of "per day" in item 8, and thus this was changed to "each day").

The Fear of Cancer Recurrence Inventory – Parent version (FCRI-P)

The FCRI-P was adapted from the existing FCRI-Caregiver version (Lin et al., 2018; Simard & Savard, 2009). The caregiver measure is identical to the FCRI-SF patient self-report measure, except the wording refers to one's fear about a significant other's cancer recurring (e.g., "*I am worried or anxious about the possibility of my significant other's cancer recurrence*"). For the FCRI-P, items from the FCRI-Caregiver were modified to reflect parents' fear that their child's cancer could return (e.g., *"I am worried*

or anxious about the possibility of my child's cancer recurrence"). No other changes were made.

4.3.3. Measures

Demographics

Demographic and medical characteristics were self-reported by children or parents or abstracted from children's medical records.

Intolerance of Uncertainty Scale – Parent (IUS-12) and Child (IUS-C) versions

Parents and children completed the 12-item IUS-12 (Carleton et al., 2007) and IUS-C (Boulter et al., 2014), respectively. Both measures evaluate individuals' own emotional, cognitive, and behavioural reactions to uncertain situations and events. Each item is rated on a 5-point scale ranging from 1 ("not at all characteristic of me/not at all like me") to 5 ("entirely characteristic of me/entirely like me"). Items are summed to derive a total score with higher total scores indicating greater intolerance of uncertainty. Internal consistency was excellent for the IUS-12 ($\alpha = .91$) and IUS-C ($\alpha = .90$).

Pain Catastrophizing Scale – Parent (PCS-P) and Child (PCS-C) Versions

Parents completed the PCS-P (Goubert et al., 2006) and children completed the PCP-C (Crombez et al., 2003), which assess individuals' tendencies to magnify the threat value, ruminate about, and feel helpless in the face of pain. The PCS-P assesses parents' thoughts about when their child is in pain, and the PCS-C assesses children's own thoughts about when they are in pain. Each of the 13 items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). Items are summed to derive a total score with higher scores indicating a greater tendency to catastrophize about pain. Internal consistency was excellent for the PCS-P ($\alpha = .95$) and PCS-C ($\alpha = .92$).

Body Vigilance Scale – Child Version (BVS-C)

The BVS-C (Boyer et al., 2006) assesses children's attentional focus to internal bodily sensations. Three items assess children's degree of attentional focus, sensitivity to changes in bodily sensations, and time spent attending to bodily sensations. Children indicate, on an 11-point scale, the degree to which each statement is like them ranging from 0 ("not at all like me") to 10 ("a lot like me"). Item scores are divided by 10 and then summed to create a total score, with higher scores indicating greater attentional focus to bodily sensations. Internal consistency was acceptable ($\alpha = .74$).

Healthcare Utilization

Healthcare utilization was assessed using questions modified from a previous study (Lebel et al., 2013). Parents reported on the number of times in the past year that: (a) they contacted a doctor or nurse by email or telephone regarding a symptom, illness, or medical condition their child may have had; (b) their child had an appointment with any doctor or nurse; and (c) their child visited the emergency department of any hospital. Parents selected one of the options to answer question: 0 times, 1-2 times, 3-4 times, 5-6 times, 7-10 times, or >10 times.

4.3.4. Statistical Analyses

Analyses were performed using SPSS v26.0. Descriptive statistics were used to examine the item properties and normality assumptions for each item. Exploratory factor analysis (EFA) using iterated principal axis factoring with oblique rotation was used to examine the underlying factor structures of the FCRI-C and FCRI-P. EFA was used because an exploratory approach was needed to examine the performance of adapted items in a new population. Criteria used to select a factor structure included eigenvalues

>1, primary factor loadings, interpretability, and overall variance accounted for (Costello & Osborne, 2005; Tabachnick & Fidell, 2013). Internal consistency was examined with Cronbach's alpha coefficient. Pearson's correlation coefficients assessed the relationship between parent and child FCR, demographic factors, and measures of construct validity. Effect sizes were defined as: <0.3 weak; 0.3-0.5 moderate; >0.5 strong (Cohen, 1988). The relationship between parent and child FCR and healthcare utilization was examined using Kendall's τ_b. Paired samples *t*-tests compared FCR scores between parent-child dyads. Independent samples *t*-tests compared FCR scores between male and female survivors.

4.4. Results

4.4.1. Item Properties, Internal Consistency, and Factor Analysis

FCRI-Child Version

Responses covered the full possible range of scores (0-4) for all items. The skewness and kurtosis scores for all items were acceptable (i.e., skew < 3.0 and kurtosis < 7.0) (Byrne, 2010; Kline, 2016). Examination of the item-total correlations revealed that the reverse-scored item (#5) did not correlate highly with the other items (corrected item-total correlation <.30). This is congruent with recent examinations of the factor structure of the adult FCRI (Costa et al., 2016; Lebel, Simard, et al., 2016). To maximize the comparability of the FCRI-C to the adult FCRI-SF, this item was retained for the factor analysis. The EFA produced a one-factor solution explaining 53.3% of the variance. Item factor loadings were excellent (> .70), except for item #5 which had a loading of .25 (Table 1). The internal consistency of the 9-item scale was good (α = .88). The sample mean for the FCRI-C total score was 10.10 (*SD* = 7.9, range 0-29).

FCRI-Parent Version

Responses covered the full possible range of scores (0-4), except for items #3 (range: 1-4) and #8 (range: 0-2). The skewness and kurtosis scores for all items were acceptable. Examination of the item-total correlations revealed that all corrected item-total correlations were adequate (>.3). Based on the criteria of eigenvalues >1, the initial EFA resulted in a two-factor solution. Six items cross-loaded on both factors, five of which loaded more strongly onto one single factor. The exception was the reverse-scored item (#5) which had a slightly stronger loading on the second factor. The EFA was repeated with a forced one-factor solution to examine a more parsimonious model. The one-factor model was a good fit to the data, explaining 41.1% of the variance. The primary factor loadings of eight items was strong (>.5) and the loading of item #5 was acceptable (Table 2). The internal consistency of the 9-item scale was good (α=.83). The sample mean for the FCRI-P total score was 17.44 (*SD* = 6.49, range 5-31).

Survivors of childhood cancer reported significantly lower levels of FCR on the FCRI-C compared to their parents on the FCRI-P ($t(98)=-8.12$, $p<.001$). FCRI-C and FCRI-P total scores were not significantly correlated ($r = .20$, $p = .053$).

4.4.2. Association with Demographic Factors

FCRI-Child Version

There were no significant associations between the FCRI-C and child current age, age at diagnosis, or time off treatment (Table 3). Girls scored higher on the FCRI-C compared to boys (FCRI-C total score means ± SD for girls and boys: 11.68 ± 8.96 vs. 8.88 ± 6.72) however the difference was not statistically significant ($p = .058$).

FCRI-Parent Version

Parent FCR was not associated with child current age, age at diagnosis or time off treatment (Table 4). Parents of female survivors reported slightly higher FCRI-P scores compared to parents of male survivors (FCRI-P total score means ± SD for parents girls and boys: 18.18 ± 6.76 vs. 16.84 ± 6.26) however the groups were not statistically different (p = .30).

4.4.3. Construct Validity

Measure means (*SD),* Pearson's correlation coefficients, and sample sizes are listed in Tables 3, 4, and S2.

FCRI-Child Version

For children, greater intolerance of uncertainty, body vigilance, and tendency to catastrophize about pain were all moderately (r = .40-.47) associated with higher total scores on the FCRI-C (Table 3).

FCRI-Parent Version

For parents, greater intolerance of uncertainty and tendency to catastrophize about their child's pain were moderately (r=.39-.46) associated with higher total scores on the FCRI-P (Table 4).

4.4.4. Criterion Validity

Parent FCR was positively related to the number of times their child's doctor or nurse was contacted (τ_b = .34, p<.01) and number of appointments with a doctor or nurse (τ_b = .28, p<.01), but not emergency department visits (p>.05). Child FCR was not related to any healthcare utilization variables (ps all >.05; Table S3).

4.5. Discussion

The aims of this study were to develop and examine the initial psychometric properties of the Fear of Cancer Recurrence Inventory Child (FCRI-C) and Parent (FCRI-P) versions. The FCRI-C and FCRI-P demonstrated good reliability and validity. This study offers preliminary data to support the use of the FCRI-C and FCRI-P to measure FCR in survivors of childhood cancer aged 8-18 years and their parents.

In line with recent studies examining the factor structure of the FCRI in adult survivors (Costa et al., 2016; Lebel, Simard, et al., 2016), the reverse scored item performed poorly as part of the FCRI-C with a low item-total correlation and weak factor loading. The item performed slightly better on the parent version of the measure, however still loaded relatively weakly compared to the others. In the original validations of the FCRI the authors opted to retain the item despite its poor performance to detect automatic response bias (Lebel, Simard, et al., 2016; Simard & Savard, 2009). The item may also offer important clinical information about a patient's understanding of their illness and risk for recurrence. For these reasons, and to optimize the comparability of the child and parent versions with the existing adult measure, the item was retained.

The results of the current study provide preliminary support for the construct validity of the FCRI-C and FCRI-P. Higher scores on the FCRI-C and FCRI-P were associated with greater intolerance of uncertainty for children and parents, respectively. Intolerance of uncertainty is a core feature of anxiety disorders (Einstein, 2014) and a key mechanism proposed to underlie the development and maintenance of FCR (Fardell et al., 2016). There is also mounting evidence to suggest that survivors with elevated FCR report hypervigilance and worry about bodily symptoms, such as pain and fatigue

(Cunningham et al., 2021; Mutsaers et al., 2016). In this study, higher scores on the FCRI-C were positively associated with children's attention to their bodily symptoms. Further, children and parents who scored higher on the FCRI-C and FCRI-P reported a greater tendency to catastrophize about their pain and their child's pain. The relationships between child and parent FCR and these theoretically-supported factors lends credit to the construct validity of the FCRI-C and FCRI-P.

Contrary to the adult FCR literature, the FCRI-C and FCRI-P were not related to any child demographic factors. In adult survivors, those who are younger and female generally report higher levels of FCR (Simard et al., 2013). While there was a trend towards higher levels of FCR in female survivors and parents of female survivors, the effect was not significant. It is possible that this study was underpowered to detect sex differences, or that the difference becomes more pronounced later in development.

In adult cancer survivors, elevated FCR is linked with increased outpatient and emergency visits (Champagne et al., 2018; Lebel et al., 2013). In this study, parent, but not child, FCR was related to the number of times the child's doctor or nurse was contacted, and the number of outpatient medical appointments a child had in the past year. Parent FCR was significantly higher than child FCR, and so is possible that the relationship observed between parent FCR and healthcare use may reflect parents efforts to seek reassurance about their child's health to alleviate their own fears. Healthcare utilization is also a more distal process for children as they must rely on others (e.g., parents) as an intermediary to initiate contact with the healthcare system.

Widespread use of the FCRI-SF in the adult cancer survivorship literature has been due in part to its utility as a screening measure to identify those with clinical levels

of FCR. A recent meta-analysis of 33 studies using the FCRI-SF in adults found that the weighted mean score across studies was 15.7, with 53.9% of survivors reporting scores above the cutoff of ≥ 13 (A. B. Smith et al., 2020). In the current study, mean levels of FCR for child survivors were significantly lower than the adult literature, meaning that, on average, survivors of childhood cancer may experience less severe FCR than adult survivors. This finding is supported by a recently proposed theoretical framework suggesting that children's experience of FCR may be less severe early in childhood and adolescence given their stage of cognitive and social development (Tutelman & Heathcote, 2020). That said, total scores on the FCRI-C did range from 0-29 and 32.3% of children had scores ≥ 13, meaning that some children do experience FCR at high levels. The validity of the adult cut-off score in children is unclear and should be assessed in future studies.

Caregivers of adult survivors has generally experience higher levels of FCR compared to survivors (Hodges & Humphris, 2009) and the same was true in the current study; parents' average scores on the FCRI-P were significantly higher than their child's scores on the FCRI-C and as a group were above the ≥ 13 FCRI-SF cut-off. This finding is consistent with past research which has found that parents of survivors experience greater distress, such as symptoms of post-traumatic stress, than the survivors themselves (Kazak et al., 2004). During survivorship, the primary responsibility for a child's health is shifted from clinicians to parents, and they must monitor their child for signs of recurrence. Parents may also feel the need to "stay strong" for their child and therefore may not have had the opportunity to seek support for their own fears and concerns.

While parent psychosocial functioning is often a key predictor of child outcomes (Bakula et al., 2019), parent and child FCR were only weakly and not significantly correlated in the current study. It is possible that this study was not sufficiently powered to identify a small relationship between parent and child FCR, however there are also a number of other contextual factors that may explain these findings. For instance, this study captured parent and child FCR at a moment in time and may fluctuate based on situational factors (e.g., prior to scans, cancer anniversaries) (Simonelli et al., 2017). Parent and child FCR may be more closely related during times when FCR is triggered, perhaps via how parents and children communicate (Murphy et al., 2021). Conversely, parent and child self-report of FCR on a questionnaire may be a more accurate representation of their own feelings without external influence, such as parents feeling the need to act brave in front of their children, or children feeling more fearful because of their parents. Characterization of the relationship between parent and child FCR over time and across contexts will be crucial to the understanding of FCR in survivors of childhood cancer.

4.5.1. Limitations

This study has limitations which point towards directions for future research. First, while this study recruited children ages 8-18 years, the average age of the sample was 14.58 years, and there were fewer pre-adolescent participants. Further studies are needed to assess the reliability and validity of the FCRI-C in younger children (aged 8-11 years). Additionally, FCR also includes the possibility that cancer could progress (Lebel, Ozakinci, et al., 2016), so future studies should examine FCR in children still receiving treatment. Moreover, the criterion and construct validity of the FCRI-C and FCRI-P

should be further explored; particularly relevant are associations with quality of life, anxiety and depression. Finally, the sample size of the study was modest and the available sample for some measures of construct and criterion validity was relatively small.

4.5.2. Clinical Implications

While additional validation is necessary, the FCRI-C and FCRI-P could be used both clinically and in research to better understand the experience of FCR in survivors of childhood cancer and parents. While most survivors reported low levels of FCR, there is a subset with higher levels that may require intervention. Parent levels of FCR were high overall flagging this group as high priority for clinical attention.

4.5.3. Conclusions

This research describes the development and preliminary validation of measures to assess FCR in survivors of childhood cancer (FCRI-C) ages 8-18 years and their parents (FCRI-P). The FCRI-C and FCRI-P demonstrated strong reliability and validity. These measures will allow for the examination of priority research questions, such as the prevalence, risk factors, and consequences of FCR in survivors of childhood cancer. Future research should examine the psychometric properties of the FCRI-C and FCRI-P and clinical cut-off scores in a separate sample.

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4.7. Conflicts of Interest

The authors report no conflicts of interest.

4.8. Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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4.10. Tables

Table 4.1. FCRI-C Factor Loading

Item	Factor Loading
I am worried about the possibility of having cancer again	.77
I am afraid of having cancer again	.77
It is normal for me to be worried about the possibility of having cancer again	.69
When I think about the possibility of having cancer again, I think about other bad things that could happen (like dying, or the impact on my family)	.79
I am cured and the cancer will not come back	.25
In your mind, what is your risk of having cancer again?	.73
How often do you think about the possibility of having cancer again?	.83
How much time each day do you think about the possibility of having cancer again?	.84
How long have you been thinking about the possibility of having cancer again?	.72

Table 4.2. FCRI-P Factor Loading

Item	Factor Loading
I am worried or anxious about the possibility of my child's cancer recurrence	.82
I am afraid of my child's cancer recurrence	.79
I believe it is normal to be worried or anxious about the possibility of my child's cancer recurrence	.53
When I think about the possibility of my child's cancer recurrence, this triggers other unpleasant thoughts or images (such as death, suffering, the consequences for my family)	.63
I believe that he/she is cured and that the cancer will not come back	.34
In your opinion, is he/she at risk of having a cancer recurrence?	.59
How often do you think about the possibility of your child's cancer recurrence?	.74
How much time per day do you spend thinking about the possibility of your child's cancer recurrence?	.68
How long have you been thinking about the possibility of your child's cancer recurrence?	.51

Table 4.3. Pearson's Intercorrelations, Means, and SDs for Child Variables

	1	2	3	4	5	6	7	*M*	*SD*	*n*
1. FCRI – Child	-	.12	.06	.03	.47**	.40**	.46**	10.10	7.87	124
2. Child current age		-	.47**	.23**	.12	.34**	-.11	14.58	2.90	124
3. Child age at diagnosis			-	-.69**	.08	.09	-.04	7.06	4.61	124
4. Child Time off treatment				-	.05	.16	-.07	6.32	4.06	124
5. Intolerance of uncertainty – Child					-	.31**	.39**	28.07	11.24	122
6. Body vigilance – Child						-	.53**	12.74	6.51	113
7. Pain catastrophizing – Child							-	14.09	10.55	64

Note. Healthcare utilization variables are shown in the supplementary materials. ** $p < .01$, * $p < .05$

Table 4.4. Pearson's Intercorrelations, Means, and SDs for Parent Variables

	1	2	3	4	5	6	*M*	*SD*	*n*
1. FCRI – Parent	-	-.15	-.09	.10	.39**	.46**	17.44	6.49	106
2. Child current age		-	.43**	.30**	-.14	.06	13.88	2.97	106
3. Child age at diagnosis			-	-.66**	-.07	.23	6.19	4.42	103
4. Child time off treatment				-	-.04	-.19	6.66	4.18	103
5. Intolerance of uncertainty – Parent					-	.48**	27.63	8.65	106
6. Pain catastrophizing – Parent						-	22.51	11.60	71

Note. Healthcare utilization variables are shown in the supplementary materials. ** $p < .01$, * $p < .05$

4.11. Supplementary Materials

Supplementary Materials - Appendix A

Demographic Characteristics

Characteristics	Children (*N*=124)	Parents (*N*=106)
Current age, mean (*SD*) range, y	14.58 (2.90) 8.42-18.0	45.43 (7.02) 27.67-63.92[a]
Sex, no. female (%)	54 (43.5)	84 (92.3)[b]
Age at diagnosis, mean (*SD*) range, y	7.06 (4.61) .17-17.0	-
Time off treatment, mean (*SD*) range, y	6.32 (4.06) .83-16.50	-
Diagnosis, no. (%)		
Leukemia	63 (50.8)	-
Lymphoma	19 (15.3)	-
Solid tumor	39 (31.5)	-
CNS tumor	3 (2.4)	-
Race no. (%)[c]		
White	85 (69.1)	75 (73.5)
Asian American	17 (13.8)	8 (7.8)
Latin American	5 (4.1)	0 (0)
First Nations	3 (2.4)	3 (2.9)
Other[d]	13 (10.6)	16 (15.7)
Parent role, no. (%)[e]	-	
Mother	-	82 (90.1)
Father	-	7 (7.7)
Other[f]		2 (2.2)
Parent education, no. (%)[g]		
Did not complete high school	-	3 (3.3)
High school graduate	-	7 (7.8)
Attended trade school/community college	-	15 (16.7)
Attended university	-	36 (40.0)
Graduate school/professional training	-	29 (32.2)

Note. CNS = central nervous system. [a]Data available for 87 parents. [b]Data available for 91 parents. [c]Data available for 123 children and 102 parents. [d]Other race categories for children and parents included mixed race, Southeast Asian, Hawaiian Native or Pacific Islander. [e]Data available for 91 parents. [f]Other role included the child's aunt. [g]Data available for 90 parents.

Supplementary Materials - Appendix B

Frequency of Parent-Reported Child Healthcare Utilization (*N*=57)

Variable	Frequency, no. (%)
Contact with doctor or nurse[a]	
0 times	21 (37.5)
1-2 times	21 (37.5)
3-4 times	8 (14.3)
5-6 times	4 (7.1)
7-10 times	2 (3.6)
>10 times	0 (0)
Appointments with doctor or nurse	
0 times	4 (7.0)
1-2 times	19 (33.3)
3-4 times	21 (36.8)
5-6 times	9 (15.8)
7-10 times	4 (7.0)
>10 times	0 (0)
Visits to emergency department	
0 times	40 (70.2)
1-2 times	15 (26.3)
3-4 times	1 (1.8)
5-6 times	1 (1.8)
7-10 times	0 (0)
>10 times	0 (0)

[a]Data available for 56 participants.

Supplementary Materials - Appendix C

Kendall's Tau-b correlation coefficients between FCRI-C and FCRI-P and Healthcare Utilization Variables

	Contact with doctor or nurse (*N*=56)	Appointments with doctor or nurse (*N*=57)	Visits to emergency department (*N*=57)
FCRI-C	.09	.02	.16
FCRI-P	.34**	.28**	.16

Note. FCRI-C = Fear of Cancer Recurrence Inventory – Child version. FCRI-P = Fear of Cancer Recurrence Inventory – Parent version. ** $p < .01$

CHAPTER 5: PAIN AND FEAR OF CANCER RECURRENCE IN SURVIVORS OF CHILDHOOD CANCER

The manuscript prepared for this study is presented below. Perri Tutelman, under the supervision of Dr. Christine Chambers, was responsible for developing the research question, methodology and analytic approach, and obtaining ethical approval and funding. She developed the study protocol and data collection procedures, contributed substantially to data collection, and oversaw staff and volunteers who contributed to these activities. Ms. Tutelman was the lead on data analysis and interpretation, with the support of her co-authors, and wrote the initial draft of the manuscript. Prior to submission, she received and incorporated feedback from the study's co-authors. The manuscript was submitted to the *Clinical Journal of Pain* on October 13, 2021. The current reference for this manuscript is:

Tutelman, P.R., Chambers, C.T., Noel, M., Heathcote, L.C., Fernandez, C.V., Flanders, A., MacLeod, J., Sherry, S.B., Simard, S., Stern, M., Stewart, S.H. & Urquhart, R. (submitted). Pain and Fear of Recurrence in Survivors of Childhood Cancer. *Clinical Journal of Pain.*

5.1. Abstract

Purpose: Theoretical models suggest that anxiety, pain intensity, and pain catastrophizing are implicated in a cycle that leads to heightened fear of cancer recurrence (FCR). However, these relationships have not been empirically examined. The purpose of this study was to examine the relationships between anxiety symptoms, pain intensity, pain catastrophizing, and FCR in childhood cancer survivors and their parents and to examine whether pain catastrophizing predicts increased FCR beyond anxiety symptoms and pain intensity.

Methods: Participants were 54 survivors of various childhood cancers (M_{age}=13.1, range=8.4-17.9 years, 50% female) and their parents (94% mothers). Children reported on their pain intensity in the past 7 days. Children and parents separately completed measures of anxiety symptoms, pain catastrophizing, and FCR.

Results: Higher anxiety symptoms was associated with increased pain intensity, pain catastrophizing, and FCR in childhood cancer survivors. Higher anxiety symptoms and pain catastrophizing, but not child pain intensity, were associated with FCR in parents. Hierarchical linear regression models revealed that pain catastrophizing predicted unique variance in both parent and child FCR over and above the effects of their own anxiety symptoms and child pain.

Conclusions: This study provides novel data on the association between pain and FCR and suggests that a catastrophic style of thinking about pain is more closely related to heightened FCR than one's anxiety symptoms or the sensory pain experience in both childhood cancer survivors and their parents. Pain catastrophizing may be a novel intervention target for survivors and parents struggling with fears of recurrence.

5.2. Introduction

Five-year survival rates for childhood cancers now exceed 80%, representing a 50% increase from the 1970's (Siegel et al., 2021). While reaching survivorship is a critical milestone, survivors of childhood cancer face a lifetime of physical and psychosocial challenges. Over two-thirds of survivors of childhood cancer between the ages of 5-19 years live with a chronic health condition (S. M. Phillips et al., 2015), including chronic pain (Patton et al., 2021; Tutelman et al., 2018). They also face the ongoing possibility that their cancer could return and often monitor bodily symptoms, such as pain, for possible signs of recurrence. Monitoring pain after cancer is a fine balance between being appropriately vigilant and being hypervigilant, as the harms of hypervigilance could exceed the benefits (Heathcote et al., 2018).

Fear of cancer recurrence (FCR), defined as, "the fear, worry, or concern about cancer returning or progressing" (Lebel, Ozakinci, et al., 2016), is one of the most prevalent unmet needs reported by survivors (Simard et al., 2013) and has received a great deal of attention in the adult survivorship literature. Considerable research has found that FCR in adult survivors and their caregivers is associated with higher levels of anxiety and depression symptoms (Simard et al., 2010), more emergency and outpatient medical visits (Champagne et al., 2018; Lebel et al., 2013), greater use of psychotropic medication (Champagne et al., 2018), and lower quality of life (van den Beuken-van Everdingen et al., 2008), with caregivers reporting higher FCR than patients (Mellon et al., 2007). The number of studies examining FCR in survivors of childhood cancer and their parents is small; however, recent research has yielded findings generally congruent with the adult literature. While child survivors seem to experience FCR at a lower level

as compared to adult survivors (Tutelman, Chambers, Heathcote, et al., 2021), a significant minority of survivors of childhood cancer report high levels of FCR (Tutelman, Chambers, Heathcote, et al., 2021), which has been linked with greater post-traumatic stress (Koutná et al., 2021), more anxiety (Cunningham et al., 2021) and depression (Wroot et al., 2020) symptoms, catastrophizing about physical symptoms (Cunningham et al., 2021; Tutelman, Chambers, Heathcote, et al., 2021), and worse quality of life (Cunningham et al., 2021). Parent FCR is associated with their own intolerance of uncertainty (Tutelman, Chambers, Heathcote, et al., 2021), anxiety (Clever et al., 2018) and depression (Clever et al., 2018; Peikert et al., 2021) symptoms, lower quality of life (Clever et al., 2018; Peikert et al., 2020), catastrophizing about their children's physical symptoms (Tutelman, Chambers, Heathcote, et al., 2021), and increased use of healthcare services for their children (Tutelman, Chambers, Heathcote, et al., 2021). The burden of FCR in survivors of childhood cancer and their families underscores the importance of identifying predictors of FCR in this population to inform effective intervention strategies.

A growing body of research points to physical pain after cancer as a key predictor of the cognitive processes implicated in FCR. Research in adult survivors has established a link between pain intensity and FCR (Janz et al., 2011; van den Beuken-van Everdingen et al., 2008) and initial qualitative studies suggest that *child* survivors and their parents also worry about pain as a potential sign of recurrence (Heathcote et al., 2021; Tutelman et al., 2019). These findings are supported by one quantitative study to date which reported that pain is the symptom that survivors most commonly worried about as a sign of potential recurrence (Cunningham et al., 2021). While pain is often a symptom that

precedes diagnosis (Miser et al., 1987) and may be a worrisome sign that cancer has returned, there are many reasons why survivors of childhood cancer may experience pain. For instance, the pathophysiology of cancer and the intensity of its treatment inherently place cancer survivors at risk for pain due to the susceptibility of the developing nervous system to neurotoxic therapies (Kandula et al., 2018), repeated skin breaking procedures and surgeries (Weisman et al., 1998), and the underlying disease process (De Martino et al., 2019). Pain is also part of living a healthy, active life after cancer (e.g., pain due to everyday bumps and scrapes, headaches, physical activity and menstruation). Due to its vague and non-specific nature, it can be challenging for survivors and their families to determine whether pain may be due to a late effect of treatment, a benign everyday cause, or a possible recurrence, and some survivors and families may automatically jump to thinking worst (i.e., catastrophizing). Despite the salience of pain and FCR for survivors of childhood cancer, there is very little empirical data examining the relationship between the two and none that examine pain as a possible predictor of FCR severity.

There are numerous theoretical models that seek to explain the relationship between pain and FCR in cancer survivorship (Fardell et al., 2016; Hall et al., 2019; Heathcote & Eccleston, 2017). In particular, the Cancer Threat Interpretation (CTI) model posits that pain may be a conditioned fear cue for some survivors as they may have learned that it was associated with a life-threatening illness in the past (Heathcote & Eccleston, 2017). Thus, some survivors may be primed to be hypervigilant to physical sensations of pain as a sign of recurrence, leading to a cycle of increased pain intensity, catastrophizing about pain, and FCR. Individual differences in affective and cognitive factors have been emphasized as important characteristics that may predispose

individuals to heightened FCR in this context (Fardell et al., 2016; Heathcote & Eccleston, 2017).

Affectively, anxiety symptoms are a key factor associated with both FCR (Simard et al., 2013) and pain (Pavlova et al., 2021). Aspects of anxiety (e.g., worry) involve repetitively thinking about feared events (Borkovec et al., 1998). From this perspective, some level of anxiety has a survival-promoting, protective function in the context of cancer survivorship. However, survivors with high levels of anxiety, as measured by anxiety symptoms, are likely primed to have more severe fears about recurrence that are no longer adaptive. Anxiety is also central to the child's experience of pain; children with higher anxiety often report greater pain intensity (Williams et al., 2015). Children's pain intensity can also be impacted indirectly as a result of their *parent's* anxiety. Parents with higher anxiety can inadvertently engage in protective behaviors (e.g., attention to pain) (Sieberg et al., 2011) that increase their child's pain (Clementi et al., 2019; Lynch-Jordan et al., 2018). For survivors of childhood cancer, it is possible that their own and their parents' anxiety symptoms may predispose them to experience more pain, leading both individuals to have a more catastrophic style of appraising the pain, and ultimately, exacerbating fears of recurrence.

Pain catastrophizing is an important cognitive style to consider in the context of pain and FCR in survivors of childhood cancer. Pain catastrophizing is the tendency to magnify the threat value, ruminate about, and feel helpless in the face of pain (Sullivan et al., 2001) and is a robust predictor of adverse outcomes (e.g., increased pain intensity, distress) in children (Feinstein et al., 2017; Lynch-Jordan et al., 2013) and parents (Caes, Vervoort, et al., 2014). Despite its associations with pain intensity, pain catastrophizing

explains unique variance in child outcomes beyond the effect of pain intensity (Vervoort et al., 2006). The way children and parents think about pain may be more closely related to FCR than anxiety symptoms and the sensory experience of pain itself.

Based on theoretical and empirical work it is conceivable that anxiety symptoms, pain intensity, and pain catastrophizing are implicated in a cycle that leads to heightened FCR in survivors of childhood cancer and their parents. However, the relationships among these variables have not been explicitly examined in cancer survivors, adult or child. Thus, the objectives of this study were to: (1) examine the relationships between anxiety symptoms, child pain intensity, pain catastrophizing, and FCR in children cancer survivors and their parents; and (2) examine whether pain catastrophizing predicts FCR over-and-above anxiety symptoms and pain intensity among children and parents. It was hypothesized that (1) anxiety symptoms, child pain intensity, pain catastrophizing, and FCR would be significantly correlated in both children and parents; and (2) pain catastrophizing would explain unique variance in FCR over-and-above anxiety symptoms and pain intensity for children and parents.

5.3. Method

Data were collected as part of a larger program of research examining pain and FCR in childhood cancer survivors examining distinct research questions. This paper examines relationships between anxiety symptoms, pain intensity, pain catastrophizing, and FCR in survivors of childhood cancer and their parents. A second paper from this program examined patterns of sensory processing in survivors of childhood cancer (Tutelman, Chambers, Cornelissen, et al., 2021) and another examined the psychometric

properties of the Fear of Cancer Recurrence Inventory– Parent (FCRI-P) and Child (FCRI-C) versions (Tutelman, Chambers, Heathcote, et al., 2021).

5.3.1. Participants

Survivors of childhood cancer and one of their parents were recruited from the IWK Heath Centre's pediatric hematology/oncology database. The IWK Health Centre is a tertiary care referral centre serving a population of 1.8 million in Maritime Canada. Children and their parents were eligible to participate if: (a) the child was between the ages of 8-17, was diagnosed with cancer, completed treatment, and had not experienced a recurrence or secondary cancer, (b) both the parent and child agreed to participate, and (c) both the parent and child could read and understand English. Children were excluded if they had a medical condition with an associated pain manifestation unrelated to their cancer (e.g., juvenile idiopathic arthritis) or had cognitive difficulties that, according to their parents, would impact their ability to participate.

Of the 156 families invited, 57 (37%) consented to participate. Three children did not complete the study questionnaires. Thus, the sample comprised 54 survivors of childhood cancer (M_{age}=13.1, range=8.4-17.9 years, 50% female) and one of their parents (94% mothers). Almost all children (93%) and parents (94%) identified as White. Approximately half (51%) of the sample had a history of leukemia. On average, children completed treatment 7.0 years before participating (range=1.2-16.5 years) and were diagnosed at 5.0 years of age (range .17-13.75 years). Full demographic and medical characteristics are shown in Table 1.

5.3.2. Procedure

The IWK Research Ethics Board approved this study (#1022720). Potential participants were sent a letter introducing the study by an oncology clinician. Study staff then followed up by telephone to provide more information and confirm eligibility. Interested children and their parents visited the research laboratory where they completed questionnaires separately. Written informed parental consent and child consent (ages 13-17 years) or assent (ages 8-12 years) was obtained by a study research assistant prior to participation. Honoraria were provided to children and parents. This study employed principles of patient-oriented research, including engagement of patient partners who were young adult survivors of childhood cancer throughout the research process (Patient-Centered Outcomes Research Institute, 2016).

5.3.3. Measures

Demographics

Parents reported on their child's age, sex, and race. They also reported on their own sex, race and their relationship to their child. Child clinical variables (e.g., diagnosis and treatment information) were abstracted from medical records.

Child pain

Children reported on their pain characteristics using the valid and reliable Pain Questionnaire (Palermo et al., 2004). Children were asked to report the frequency with which they experienced pain in the last 7 days on a 5-point Likert scale ranging from 0 ("not at all") to 4 ("daily"). Children indicated the location of their body with the most pain on a body map. Average intensity of pain experienced in the past 7 days was rated on an 11-point numerical rating scale ranging from 0 ("no pain") to 10 ("the worst pain

you could ever imagine"). Children reported how long they have experienced pain on a 4-point Likert scale ranging from 0 ("just this month") to 3 ("over a year").

Pain catastrophizing – Parent (PCS-P) and Child (PCS-C) versions

Parents and children reported on their tendency to magnify the threat value, ruminate about, and feel helpless in the face of pain using the Pain Catastrophizing Scale, Parent (PCS-P) (Goubert et al., 2006) and Child (PCS-C) (Crombez et al., 2003) versions, respectively. The PCS scales are valid and reliable measures that assess parents' thoughts when their child is in pain (PCS-P) and children's thoughts when they are in pain (PCS-C). Each measure contains 13 items that are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). Items are summed for a total score ranging from 0-52 with higher total scores reflecting a higher level of catastrophizing. The internal consistency in the present sample was excellent for parents ($\alpha = .96$) and children ($\alpha = .92$).

Fear of cancer recurrence – Parent (FCRI-P) and Child (FCRI-C) versions

Parents and children reported on their fear of cancer recurrence using the Fear of Cancer Recurrence Inventory – Parent (FCRI-P) and Fear of Cancer Recurrence Inventory – Child (FCRI-C) versions (Simard & Savard, 2009; Tutelman, Chambers, Heathcote, et al., 2021). The FCRI-P and FCRI-C are valid and reliable measures that evaluate the presence, frequency, intensity, and duration of thoughts about fear of cancer recurrence. The FCRI-P measures parents' fears about their child's recurrence and the FCRI-C measures children's fears about their own recurrence. Each measure contains nine items that are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("a great deal"), with total scores ranging from 0-36. Higher scores indicate greater fear about

recurrence. The internal consistency in the present sample was good for parents (α = .81) and children (α = .88).

Anxiety symptoms – Child

Children's anxiety symptoms were assessed using the Anxiety Total subscale of the Revised Children's Anxiety and Depression Scale - Short Version (RCADS-A) (Ebesutani et al., 2012). Children reported how each of the 15 items applies to them on a 4-point Likert scale ranging from 0 ("never") to 3 ("always"). Total scores range from 0-45 with higher scores indicating more severe anxiety symptoms. The internal consistency of the scale was good (α = .86).

Anxiety symptoms – Parent

Parents reported on their anxiety symptoms using the Anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) (Zigmond & Snaith, 1983). The HADS-A is a 7-item validated self-report measure that assesses to presence of anxiety symptoms. Items are rated on a 4-point Likert scale ranging from 0 to 3 and summed to create a total score. Possible scores range from 0-21 with higher scores indicating more severe anxiety symptoms. The internal consistency of the scale was good (α = .87).

Intensity of treatment

The intensity of each child's cancer treatment was categorized using the Intensity of Treatment Rating Scale 3.0 (ITR-3) (Kazak et al., 2012). The ITR-3 is a validated measure that classifies the intensity of childhood cancer treatment from 1 (least intensive) to 4 (most intensive) based on diagnosis type, disease stage, and treatments received. Two independent raters coded each participant's treatment intensity. Consultation from a pediatric oncologist (C.V.F.) was sought as needed. No rating discrepancies occurred.

5.3.4. Analysis

Analyses were conducted using SPSS version 26. Descriptive statistics were used to characterize the sample on variables of interest. Pearson's correlations were conducted to assess the relationship between demographic (e.g., age) and medical (e.g., time off treatment, treatment intensity) characteristics and key variables (e.g., child pain intensity and parent and child pain catastrophizing, anxiety symptoms, and FCR). Independent samples *t*-tests were used to examine differences in key variables based on child sex.

Hierarchical regression analyses evaluated the unique contribution of pain catastrophizing to FCR beyond anxiety symptoms and pain intensity for parents and children. Demographic and medical variables significantly related with parent and/or child FCR were included as covariates in the first step of both models.

Missing data on study variables was minimal (1.62%) and was missing completely at random (Little's MCAR test $\chi^2 = 365.27$, p=.99). All included participants completed at least 80% of items on each questionnaire. Individuals' mean scores were used as a replacement for missing items.

5.4. Results

5.4.1. Descriptive statistics

Descriptive statistics for the primary study variables are in Table 2. On the ITR-3, 9% of children had treatments classified as least intensive, 32% as moderately intensive, 41% as very intensive, and 18% as most intensive. On average, parent anxiety symptoms scores were elevated, with 65% scoring above the clinical cutoff (i.e., a score $\geq$ 8 on the HADS-A) (Bjelland et al., 2002). Conversely, children's average anxiety symptoms

scores were within normal ranges, with only 22% scoring above the clinical cutoff (i.e., a score $\geq$ 12 on the RCADS-A) (Klaufus et al., 2020).

5.4.2. Pain characteristics

Of the 54 survivors in the sample, 30 (56%) endorsed experiencing pain in the past 7 days. Of those with pain, most (90%) reported having pain between 1-3 times per week; three (10%) reported having daily pain. Locations of pain included the legs/feet (60%), back (43%), head/neck (33%), arms/hands (23%), abdomen (17%) and/or chest (10%). For most survivors (70%), their pain was chronic (i.e., present for over 3 months), with 53% reporting having had pain for over a year. The average pain intensity in the past 7 days across the entire sample was 2.17/10 (*SD*=2.23). Among those with pain (*n*=30), the average intensity reported was 3.9/10 (*SD*=1.47) and ranged from 1/10 to 7/10.

5.4.3. Relationships between key variables

Pearson's correlations among the key study continuous variables for children and parents are summarized in Table 2. Younger child age at the time of participation and less time off treatment were significantly associated with higher levels of parent, but not child FCR. Children who underwent more intense treatments reported higher FCR, as did parents. Higher child FCR was associated significantly higher anxiety symptoms, self-reported pain intensity, and pain catastrophizing. Parents who reported higher FCR also reported higher levels of anxiety symptoms and tendency to catastrophize about their child's pain. Compared to male survivors (*M*=1.24/10, *SD*=2.00), females (*M*=3.01/10, *SD*=2.11) reported significantly higher levels of pain intensity ($t(52)=3.31$, $p<.01$). There were no other significant sex differences. Parent and child FCR, anxiety symptoms, and pain catastrophizing were not significantly correlated.

5.4.4. Hierarchical regression analyses

Two hierarchical regression analyses were conducted, one for child FCR and one for parent FCR (Table 3). Based on the correlational analyses, child age at participation, time off treatment, and treatment intensity were added as covariates in step 1. Anxiety symptoms was added in step 2, child pain intensity in step 3, and pain catastrophizing in step 4.

Model 1: Child FCR

Child current age, time off treatment, and treatment intensity explained 15% of the variance in child FCR in the first step of the model. However, only treatment intensity was significantly associated with child FCR in the first step. Above and beyond the covariates, anxiety symptoms accounted for an additional 12% of variance in child FCR. Adding child pain intensity in step 3 did not significantly improve the model, explaining only an additional 2% of the variance in child FCR. In the final model, child pain catastrophizing accounted for a significant proportion of unique variance (7%) in FCR beyond anxiety symptoms and child pain intensity. The final model explained 36% of variance in child FCR.

Model 2: Parent FCR

Child current age, time off treatment, and treatment intensity explained 19% of the variance in parent FCR in the first step of the model. Similar to the child model, only treatment intensity was significantly associated with parent FCR in the first step. The addition of anxiety symptoms intensity in step 2 did not significantly improve the model, nor did the addition of child pain intensity in step 3, explaining only 4% and 1% additional variance in FCR, respectively. In the fourth step, adding parent pain

catastrophizing significantly improved the model, accounting for 11% of unique variance in parent FCR. The final model explained 35% of variance in parent FCR.

5.5. Discussion

The Cancer Threat Interpretation (CTI) model suggests that anxiety symptoms, pain intensity, and pain catastrophizing are implicated in a cycle that leads to heightened fear of cancer recurrence (FCR) in cancer survivors (Heathcote & Eccleston, 2017). This is the first empirical study to test the relationships between these variables in survivors of childhood cancer and their parents. As hypothesized, higher anxiety symptoms were associated with increased pain intensity, pain catastrophizing, and FCR in survivors of childhood cancer. Higher parent anxiety symptoms and pain catastrophizing, but not pain intensity, were associated with FCR in parents of survivors. Pain catastrophizing predicted unique variance in both parent and child FCR over and above the effects of their own anxiety symptoms and child pain intensity. Results of the current study provide novel data on pain as a trigger of FCR and highlight the central contribution of catastrophic pain-related interpretations to FCR severity.

This study adds to the growing body of evidence on pain in cancer survivorship and FCR and the relationship between them. Existing research on the experience of pain after childhood cancer has varied. The prevalence of post-cancer pain has ranged from 4.3%-75%, largely due to the use of non-validated and single-item assessment tools (Alberts et al., 2018; Schulte et al., 2021). The current study used a valid and reliable pain assessment measure and found that 56% of survivors reported experiencing pain in the last 7 days. For the majority (70%) of survivors with pain, the pain was chronic (i.e., present for over 3 months). Univariate analyses revealed a significant positive

relationship between the intensity of pain experienced in the last 7 days and FCR in survivors of childhood cancer. That is, survivors who reported higher levels of pain intensity also reported higher FCR. This is in line with emerging qualitative (Heathcote et al., 2021; Tutelman et al., 2019) and quantitative (Cunningham et al., 2021; Zebrack & Chesler, 2002) work that has found that pain is perceived as a worrisome sign of recurrence by survivors of childhood cancer. Despite the relationship between child pain intensity and child FCR, child pain intensity was not associated with parent FCR. Indeed, literature examining the link between child pain intensity and parent psychosocial factors is mixed (Birnie, Chorney, et al., 2017; Pagé et al., 2013). It is possible that this study was underpowered to detect this dyadic relationship. However, pain is also an inherently internal experience that is not always communicated to, and observable by, others. Child survivors may have concealed the intensity of the pain they experienced in the past week to protect their parents from worry and distress, which has been demonstrated in samples of healthy children (Larochette et al., 2006) and may be even more salient for survivors of childhood cancer. Further research is needed to understand the dyadic context of pain and FCR in survivors of childhood cancer and their parents.

A growing body of literature argues that affective and cognitive factors related to pain can be more important predictors of child and parent outcomes than the sensory experience of pain (Fischer et al., 2019; Vervoort et al., 2006). This hypothesis was supported in the current study. After controlling for covariates, anxiety symptoms, and child pain intensity, pain catastrophizing predicted unique variance in FCR for both children and parents. Notably, this effect was observed in the absence of a significant relationship between child pain intensity and parent FCR. These findings align with the

results of recent work which found that worry about different physical symptoms was a stronger predictor of FCR than the frequency of the symptoms themselves (Cunningham et al., 2021). The current study extends past findings by examining the specific role of pain as a symptom and worry about pain (i.e., pain catastrophizing) (Eccleston et al., 2012) in both survivors of childhood cancer and their parents. Indeed, bodily symptoms serve different functions, and for pain, its role is to signal threat and mobilize individuals to avoid harm (Eccleston & Crombez, 1999). Results also suggest that catastrophizing about pain specifically may be a common factor associated with FCR in survivors of childhood cancer and their parents and a potential target for interventions.

While anxiety symptoms were related to FCR in the univariate analyses for both children and parents, only child anxiety symptoms was significant in the multivariate model after controlling for the covariates. Child treatment intensity exhibited a strong effect on parent FCR and remained a significant predictor across all steps of the model. Parents of childhood cancer survivors are at risk for post-traumatic stress for years following the completion of their child's treatment (Kazak et al., 2004) and often describe treatment-related intrusion symptoms (Tutelman et al., 2019). It is possible that fears that are more catastrophic in nature and specific to their child's health and treatment play a more important role in FCR than general anxiety symptoms. The significant contribution of parent pain catastrophizing to FCR that held beyond the effect of the covariates would also support this contention. Similarly, the effect of child anxiety symptoms on FCR was no longer significant after adding pain catastrophizing to the model. Taken together, these findings suggest that a catastrophic style of thinking about pain - the tendency to magnify the threat value of, ruminate about and perseverate on pain

- may be more closely related to FCR than one's anxiety symptoms or the sensory pain experience, which has important implications for the assessment and treatment of FCR.

There are growing efforts to implement distress screening protocols in the pediatric survivorship context. Such efforts have focused on the use of broad distress screening tools (e.g., distress thermometer) (van der Geest et al., 2018) or the use of items that assess general anxiety or depression (Pépin et al., 2021). Results of the current study align with recently published work (Cunningham et al., 2021) suggesting that the assessment of general anxiety or distress alone may be inadequate to capture the catastrophic thoughts survivors and parents have about symptoms, such as pain, which are ultimately more closely related to FCR. Clinicians should be aware of this potential cognitive process associated with FCR and refer children and/or parents presenting with heightened distress for an in-depth psychosocial assessment to evaluate the contribution of a catastrophic cognitive style, including catastrophic thoughts about pain, to their FCR.

Findings from this study point to pain catastrophizing as a novel and salient target to address FCR in survivors of childhood cancer and their parents. The pediatric chronic pain literature has shown that pain catastrophizing is a malleable construct that is highly responsive to intervention. Cognitive-behavioral strategies such as pain science education, cognitive reframing, and relaxation training seek to reduce catastrophic cognitions about pain (Coakley & Wihak, 2017), and are associated with sustained reductions in pain catastrophizing in both children (Coakley et al., 2018; Kashikar-Zuck et al., 2013; Lomholt et al., 2015) and parents (Coakley et al., 2018; Levy et al., 2017) in pediatric chronic pain populations. However, it is crucial to acknowledge a key difference between the chronic pain and cancer survivorship contexts; while many forms of chronic

pain represent functional somatic amplification, pain in cancer survivorship may be the sign of an acute and serious health concern (e.g., a recurrence or late effect). Clear communication from clinicians regarding the specific characteristics of pain a patient should be vigilant for (e.g., nighttime wakening with pain or pain that interferes with desired activities) will be essential in successfully reducing catastrophic cognitions about pain in survivorship. Indeed, several interventions to address FCR have been developed for adult survivors and include content focused on correcting disproportionate body vigilance and threat monitoring (Butow et al., 2017; Tomei et al., 2018). However, coverage of pain-specific cognitions in these interventions is unclear and pain catastrophizing has not been evaluated as a treatment outcome. Results from this study suggest that cognitive behavioral strategies that target pain catastrophizing specifically, borrowed from the pain psychology literature, will be important to include and evaluate in future FCR interventions developed for child survivors and their families.

This study had numerous strengths including the inclusion of both childhood cancer survivors and parents, use of valid and reliable measures to assess pain, anxiety, and FCR, and its theory-driven approach. Limitations should also be noted. While this study focused on the relationship between pain and FCR, survivors of childhood cancer may also view pain as a threat of other health concerns, such as late effects (Tutelman et al., 2019), which are more likely to occur than recurrence. Future research should examine the relationships between pain and other adverse outcomes in this population over time. Additionally, due to the cross-sectional and correlational design of this study, the directionality of the relationship between the variables is unknown. For example, while it is possible that pain catastrophizing leads to greater FCR, the reverse could also

be true, where children and parents with higher FCR then in turn catastrophize more about pain. Further, while results suggest the pain catastrophizing is most important to FCR, it is possible that this variable is more proximally related to FCR and that anxiety symptoms may still play an important role more distally, increasing an individual's susceptibility to increased pain and catastrophizing. Longitudinal studies with larger samples could examine the paths and mechanisms by which anxiety symptoms, pain intensity, and pain catastrophizing contribute to FCR. Finally, the current sample had little racial diversity, due to the relatively homogeneous region from which the cohort was recruited, and certain tumor groups (e.g., CNS tumors) were under-represented. As is common in survivor research, the voice of the father is under-represented. Further research with more diverse samples is needed.

In conclusion, this study examined the relationships between anxiety symptoms, child pain intensity, pain catastrophizing and FCR in survivors of childhood cancer and their parents. The findings lend support to aspects of the CTI model in that higher anxiety symptoms was associated with increased pain intensity, pain catastrophizing, and FCR in survivors of childhood cancer. For parents, greater anxiety symptoms and pain catastrophizing were associated increased FCR. Results also demonstrate that children's and parents' tendency to catastrophize about pain explains an important and unique role in FCR beyond the impact of anxiety symptoms and the sensory aspect of pain. These findings point to pain catastrophizing as a potential therapeutic target for survivors and parents struggling with fears of recurrence. These results may help survivors and their families establish a more adaptive relationship with pain after cancer.

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5.7. Tables

Table 5.1. Demographics

Characteristics	Children (*N*=54)	Parents (*N*=54)
Current age, mean (*SD*) range, y	13.5 (3.1) 8.4-17.9	44.6 (7.3) 27.7-63.9[a]
Sex, no. female (%)	27 (50)	52 (98.1)[b]
Age at diagnosis, mean (*SD*) range, y	5.0 (3.2) .2-13.8	-
Time off treatment, mean (*SD*) range, y	7.0 (4.1) 1.2-16.5	-
Diagnosis, no. (%)		
Leukemia	29 (53.7)	-
Lymphoma	4 (7.4)	-
Solid tumor	19 (35.2)	-
CNS tumor	2 (3.7)	-
Race no. (%)[c]		
White	50 (92.6)	49 (94.2)
First Nations	3 (5.6)	2 (3.8)
Other	1 (1.9)	1 (1.9)
Parent role, no. (%)[d]	-	
Mother	-	50 (94.3)
Father	-	1 (1.9)
Other[e]		2 (3.8)
Parent education, no. (%)[e]		
Did not complete high school	-	1 (1.9)
High school graduate	-	5 (9.4)
Attended trade school/community college	-	12 (22.6)
Attended university	-	21 (39.6)
Graduate school/professional training	-	14 (26.4)

Note. CNS = central nervous system.[a]Data available for 50 parents. [b]Data available for 53 parents. [c]Data available for 52 parents. [d]Data available for 53 parents. [e]Other role included the child's aunt. [e]Data available for 53 parents.

Table 5.2. Intercorrelations, means, and SD among study variables

	1	2	3	4	5	6	7	8	9	10	11	*M*	*SD*
1. Child age (years)	-	.26	.59**	-.02	-.07	-.13	.16	-.09	.08	.15	-.29*	13.52	3.14
2. Child age at diagnosis (years)		-	-.58**	-.00	-.26	.12	-.23	-.10	.28*	-.06	.08	5.01	3.23
3. Time off treatment			-	.00	.15	-.19	.24	.00	-.15	.20	-.30*	6.95	4.07
4. Intensity of treatment				-	.29*	.09	-.03	.32*	.10	.33*	.31*	2.69	.89
5. Anxiety symptoms - Child					-	-.06	.42**	.44**	.08	.43**	.13	9.31	7.20
6. Anxiety symptoms – Parent						-	-.23	-.09	.47**	.09	.30*	9.36	4.36
7. Child pain intensity (0-10)							-	.18	-.04	.30*	.08	2.17	2.24
8. Pain catastrophizing – Child								-	.14	.46**	.06	14.84	10.37
9. Pain catastrophizing – Parent									-	.01	.41**	23.94	11.96
10. Fear of cancer recurrence – Child										-	.18	10.28	7.95
11. Fear of cancer recurrence – Parent											-	19.33	6.12

** $p < .01$, * $p < .05$

Table 5.3. Hierarchical Regression Analyses for Child and Parent FCR

		Child FCR (*N*=54)			Parent FCR (*N*=54)		
		ß	R^2	ΔR^2	ß	R^2	ΔR^2
Step 1			.15	.15*		.19	.19*
	Child current age	.05			-.11		
	Time off treatment	.18			-.24		
	Treatment intensity	.33*			.30*		
Step 2			.27	.12*		.23	.04
	Child current age	.14			-.10		
	Time off treatment	.07			-.21		
	Treatment intensity	.23			.28*		
	Anxiety symptoms	.37**			.20		
Step 3			.29	.02		.24	.01
	Child current age	.12			-.09		
	Time off treatment	.06			-.25		
	Treatment intensity	.25			.28*		
	Anxiety symptoms	.30*			.22		
	Child pain intensity	.15			.13		
Step 4			.36	.07*		.35	.11**
	Child current age	.13			-.20		
	Time off treatment	.07			-.15		
	Treatment intensity	.18			.26*		
	Anxiety symptoms	.19			.04		
	Child pain intensity	.14			.12		
	Pain catastrophizing	.31*			.38**		

Note. FCR = fear of cancer recurrence. *ß*, standardized regression coefficient. Child anxiety symptoms were measured by the Revised Children's Anxiety and Depression Scale – Anxiety Total score. Parent anxiety symptoms were measured by the Hospital Anxiety and Depression Scale Anxiety subscale. Child and parent pain catastrophizing were measured by the Pain Catastrophizing Scale – Child version and Parent version, respectively. *p <.05, **p<.01.

CHAPTER 6: GENERAL DISCUSSION

The current chapter summarizes and discusses the key findings reported in Chapters 2 to 5. A discussion of the theoretical and clinical implications of the findings is then presented. An overview of the key strengths and limitations of the dissertation as well as directions for future research are provided.

6.1. Summary and Discussion of Key Findings

The overarching objective of this dissertation was to provide a comprehensive understanding of pain after childhood cancer. This objective was accomplished through four interrelated studies which used a range of qualitative and quantitative approaches. The key findings of each study, and their significance, are described below.

The aim of the first study (presented in Chapter 2) was to qualitatively explore the lived experience and meaning of pain after childhood cancer from the perspective of survivors and their parents. Using interpretive phenomenological analysis (IPA) (J. A. Smith et al., 2009), three superordinate themes were generated. The first theme was that pain is a changed experience for most children after cancer. While some children reported experiencing more frequent pain in survivorship, others reported being less sensitive to pain. Though the reasons for differences in survivors' pain frequency and tolerance are unclear, some participants speculated that factors such as nature and intensity of treatments they endured were responsible for their changed experience of pain (either more pain or less pain) in survivorship. These findings are hypothesis-generating and lay the groundwork for future research to examine why some survivors experience more pain, others less pain, and some no difference in their pain. The second theme was that pain, particularly pain that is new or ambiguous, may be interpreted by survivors and

parents as a threat of disease recurrence, late effects, or a secondary cancer. The final theme was that how children and parents interpret pain in survivorship occurs within the broader context of how children and parents appraise their cancer experience. Parents generally appraised their child's cancer and pain as more threatening than their children, which is in line with past literature demonstrating that parents of survivors often experience greater distress, including symptoms of post-traumatic stress, after the completion of their child's treatment than the survivors themselves (Kazak et al., 2004). This is perhaps due to the responsibility parents feel to monitor their child's health in survivorship, or the fact that they had to "be strong" for their children during treatment and have not yet been able to process their own fears and experiences. Further research is needed to explore these factors. Parents' functioning is important because parent appraisals played an important role in guiding how their child interpreted pain in survivorship. Taken together, the results suggest that the experience of cancer in childhood critically shapes how childhood cancer survivors and their parents experience and interpret pain. This study is an key contribution to the literature as it was the first in-depth account of the lived experience of pain after childhood cancer using a rigorous qualitative methodology. Since the completion of this study, others in the field followed (Heathcote et al., 2021). The results of this study laid the groundwork for papers 2-4 by characterizing the meaning of pain in survivors of childhood cancer and identifying factors salient to the experience (e.g., FCR, pain catastrophizing, and the role of parents).

Building on the results from Study 1, the second study (presented in Chapter 3), aimed to quantify differences in pain and sensory functioning in survivors of childhood cancer compared to published age- and sex-matched reference values. Survivors

participated in a comprehensive and validated Quantitative Sensory Testing (QST) protocol (Blankenburg et al., 2010) which evaluated their thermal and mechanical detection and pain thresholds and pain sensitivity. Almost all survivors (86%) exhibited differences to how they detect sensations and experience pain compared to published age- and sex-matched reference values (Blankenburg et al., 2010). The results of this study suggest that pervasive differences in pain and sensory functioning (decreased sensitivity, increased sensitivity, and/or pain sensitization) are present in most survivors years following the completion of treatment and add experimental pain data in support of the first theme identified in Study 1 - that pain is a changed experience after cancer. Risk factors for differences in sensory processing were identified, including demographic factors (e.g., current age, time off treatment), certain clinical factors (e.g., history of leukemia, vincristine cumulative dose, major surgery, and bone marrow/stem cell transplant) and psychosocial factors (e.g., higher anxiety and pain catastrophizing scores). Past research on pain after childhood cancer has largely relied on questionnaire-based methods. This study represents a significant advancement to the literature on pain in cancer survivorship by harnessing the utility of QST which quantifies the activity of various sensory and pain pathways at the nervous system level. The comprehensive identification of demographic, clinical, and psychosocial risk factors in this study is also an important contribution to the literature, as this may help identify survivors at greatest risk for sensory alterations, including chronic pain.

Theory (Heathcote & Eccleston, 2017) and empirical research (including results from Study 1) (Janz et al., 2011; van den Beuken-van Everdingen et al., 2008) emphasize the centrality of fear of cancer recurrence (FCR) to the experience of pain in cancer

survivorship. However, the lack of a valid and reliable self-report questionnaire to measure FCR in childhood cancer survivors (< 18 years) prevented further quantitative examination of this relationship. Thus, the aim of the third study (presented in Chapter 4) was to adapt the adult-validated Fear of Cancer Recurrence Inventory short form (FCRI) (Simard & Savard, 2009) for use with children (the FCRI-C) and parents (the FCRI-P) and to examine the psychometric properties of the adapted measures. The FCRI-C and FCRI-P both demonstrated strong internal consistency, construct validity, and criterion validity. In line with the third theme identified in Study 1 – appraisal of the cancer experience - parents reported significantly higher levels of FCR compared to children. The development of psychometrically sound measures of FCR for children and parents addresses a key gap in the literature and significantly advances the field of pediatric psychosocial oncology - allowing for the examination of priority research questions related to pain and more broadly.

Study 4 (described in Chapter 5) brought together theory (Heathcote & Eccleston, 2017) and key findings from the first three studies to examine the relationships between pain, anxiety, pain catastrophizing, and FCR in childhood cancer survivors and their parents. In line with findings from Studies 1 and 2, greater anxiety symptoms were associated with increased pain intensity, pain catastrophizing, and FCR for childhood cancer survivors. For parents, greater anxiety symptoms and pain catastrophizing, but not child pain intensity, were associated with FCR. Pain catastrophizing predicted unique variance in parent and child FCR beyond their own anxiety symptoms and child pain. Findings from this study suggest that how childhood cancer survivors and parents think about pain plays an important role in their experience of FCR. This study advanced past

research on pain and FCR in childhood cancer survivors by using valid and reliable measures of both. The study also offers innovative data linking the cognitive aspects of pain to FCR in childhood cancer survivors and parents, revealing novel intervention targets for this population.

Taken together, the body of research presented in Chapters 2-5 suggests that childhood cancer uniquely shapes the experience of pain in survivorship ranging from the lived experience (Chapter 2) and self-report (Chapter 5) of pain to the neural underpinnings of pain and sensory processing (Chapter 3). There may be certain subgroups of survivors at particular risk for changes to their experience of pain based on their demographic and clinical characteristics (Chapter 3), however this requires additional investigation and replication. Parents are likely to play an important role in children's experience of pain and FCR after cancer, qualitative evidence of which was found in Chapter 2. While parents quantitatively reported fears about their child's pain and risk for recurrence (Chapters 4-5), parent variables were not related to any child outcomes. Further research with larger and more diverse samples is needed to quantitatively assess these dyadic relationships. Across studies, psychosocial factors such as FCR (Chapters 2, 4-5), anxiety (Chapters 3,5), and pain catastrophizing (Chapters 2, 3, 5) consistently emerged as important factors associated with the experience of pain in childhood cancer survivorship. In particular, the role of cognitions about pain as a potential trigger of FCR (Chapters 2, 5) has important theoretical and clinical implications, which are described in further detail below.

6.2. Theoretical Implications

In recent years there has been growing interest in the study of pain in cancer survivorship, including the entry of new theoretical models in this field. The Cancer Threat Interpretation (CTI) model, proposed by Heathcote and Eccleston (Heathcote & Eccleston, 2017) provides a theoretical basis from which the experience of pain after cancer can be understood. The current dissertation undertook a theory-driven approach to the study of pain in cancer survivorship using the CTI model as a theoretical basis. The CTI model posits that the cancer experience may predispose survivors to negatively interpret pain as a threatening sign of disease recurrence. This negative interpretation may, in turn, make survivors hypervigilant to signals of pain, making it a more frequent and interrupting occurrence. Further, these negative interpretations of pain may drive behaviors to alleviate their FCR such as excessive healthcare seeking for reassurance or healthcare avoidance. According to the CTI model, survivors' cognitions (e.g., biased attending, catastrophizing) and affect (e.g., anxiety, distress) play a role in their experience of pain, as do factors related to the survivor's cancer history (e.g., pain as a diagnostic symptom) and the current context (e.g., can the source of the pain be determined?). Empirical research examining components of the CTI model is in its early stages. The current dissertation makes an important contribution to theory in this area by providing some of the first empirical data in preliminary support of the model and by offering novel extensions to it.

Across several studies in this dissertation, support for the relationship between pain and FCR proposed in the CTI model was found. For instance, in Chapter 5, child pain intensity in the last 7 days was moderately associated with their self-reported FCR.

At the multivariate level, child self-reported pain intensity was no longer predictive of FCR. Instead, children's negative cognitions about pain (i.e., higher pain catastrophizing) were more proximally related to FCR, emphasizing the significance of the cognitive aspects of the model. The qualitative study outlined in Chapter 2 offers important context for understanding these results. In Chapter 2, survivors described that it is generally not just any pain that leads them to have fears about recurrence, but rather, pains that are directly linked to their diagnosis (e.g., headaches for child who had a brain tumour) or pains that are new or ambiguous. These results speak to the importance of both the child's cancer history and the current context in the relationship between pain and FCR, which are factors highlighted in the CTI model.

The current dissertation also offers novel extensions to the CTI model. A key extension is the fact that survivors of childhood cancer may negatively interpret pain as a sign of other health concerns beyond recurrence. For instance, in Study 1 (Chapter 2), survivors described fearing that the pain they experience could be related to a late effect of treatment or the development of a secondary cancer. Indeed, survivors of childhood cancer are at risk for numerous late effects of treatment and these are generally more likely to occur (S. M. Phillips et al., 2015) compared to a recurrence (Wasilewski-Masker et al., 2009). Moreover, the participants in Study 1 (Chapter 2) described knowing that their risk for recurrence was generally low. The exclusive focus on FCR may overlook other more salient health concerns that survivors may fear when experiencing pain.

While the CTI model was not proposed as a pediatric-specific model, there are several important extensions for applying this model to the pediatric population. For example, while the CTI model highlights the importance of the cancer history in a

survivor's experience of pain, some children will have been diagnosed and treated for cancer at an age too young to hold firsthand autobiographical memories. This was described in Study 1 (Chapter 2) by a participant who was diagnosed and treated as an infant. In these cases, the cancer history as experienced by the survivor will be less relevant, and instead, parent and clinician narratives likely play a formative role in how child survivors interpret and experience their pain. More broadly, this dissertation highlights the importance of parents when considering pain after childhood cancer. In fact, parental influence is a component not currently addressed in the CTI model. Indeed, in Study 1 (Chapter 2), parents described fearing that their child's pain could be a sign of recurrence, even more so than the children themselves. This finding was replicated in Studies 3 and 4 (Chapters 4 and 5) with parents quantitatively reporting higher levels of FCR and pain catastrophizing than their children. While no relationship between parent and child variables were found in the current thesis (likely due to the small sample size, described in further detail below), parent psychosocial functioning is often identified as a key predictor of child outcomes (Bakula et al., 2019). That said, the current thesis does empirically link parent psychosocial functioning to behavioural outcomes relevant to children, such as healthcare utilization, where children often rely on their parents to act as intermediaries between them and the healthcare system. As reported in Study 3 (Chapter 4), parent FCR was significantly associated with increased healthcare utilization for children – a key behavioural outcome proposed in the CTI model and other models of FCR (Lebel et al., 2018; Simonelli et al., 2017). The role of parents and the potential impact that they may have on child and behavioural outcomes is a critical pediatric-

specific extension to the CTI model and the FCR field more generally (Tutelman & Heathcote, 2020).

6.3. Clinical Implications

The growing body of literature on pain and FCR, including the studies that comprise this dissertation, highlight the negative physical and psychosocial consequences that these sequalae can have on survivors of childhood cancer. Findings across studies in the current dissertation point to potential areas for clinical intervention related to pain and FCR in this population. Of note, the clinical implications described in this thesis were co-developed with patient partners and are based on both data and lived experience. This was an iterative process that entailed meeting with patient partners throughout the process of data analysis and interpretation to gain their perspectives on the meaning of the results and to contextualize the data based on their lived experience.

Study 2 (Chapter 3) offers some of the first empirical data on the pain and sensory differences survivors of childhood cancer may experience after the completion of treatment. While few survivors in the study self-reported the presence sensory symptoms, it is possible that the changes identified using QST were subclinical and may not have yet presented as clinically-reportable symptoms; the observed QST differences could nonetheless confer risk for future morbidity (e.g., chronic pain) (Lieber et al., 2018). Longitudinal studies will be important for delineating the long-term clinical relevance of such differences. Conversely, it is conceivable that survivors of childhood cancer adapt to sensory differences that occur and thus fail to identify them as clinical symptoms. Some survivors could have also been diagnosed too young to recognize a change that may occur post-treatment. The implementation of baseline sensory testing prior to the

initiation of treatment could allow for the personalized assessment of sensory changes that occur for children after treatment. Such testing has been successfully implemented in adult centres (Boyette-Davis et al., 2012) and similar baseline testing protocols, such those that assess neurocognitive functioning, have been used in pediatric settings (Sands et al., 2017). That said, children with cancer often present feeling very unwell at the time of diagnosis, and there is typically more urgency to begin treatment in the context of childhood cancer (compared to many adult cancers that tend to be more indolent in nature). These factors may affect the physiological and logistical feasibility of implementing baseline testing.

Perhaps one of the most clinically relevant implications of the results in the current dissertation is the information it can offer patients and families about the pain and sensory changes they may experience in survivorship. In Chapter 2, parents recounted the emphasis that was placed on needing to be vigilant about their child's health when they were on active treatment and discussed the difficulty of reverting to baseline levels of vigilance in survivorship. The current thesis highlights the importance of conversations between clinicians and patients about pain and sensory changes that may occur after treatment. Providing anticipatory guidance to patients and families about changes they may notice, what changes they should be concerned about, and education regarding different possible explanations (i.e., cancer recurrence is only one possible explanation), may help with coping and may be important in preventing the development of pain-related hypervigilance and pain-driven FCR in survivorship. While on the one hand it could be detrimental to raise a potential issue, such as changes to pain and sensory processing, that the patient had not identified as problematic. On the other hand, it could

be validating for patients to have clinicians bring forth potential issues, such as changes to their pain and sensory perception, as this could be something they experience but feel uncomfortable raising. Patient partners were instrumental in identifying this perspective, which is an example of the influence that engaging patient partners had in optimizing the clinical relevance of the work.

Finally, the current dissertation also has clinical implications relevant to the assessment and treatment of FCR in childhood cancer survivors and their parents. While there is growing interest in the construct of FCR in survivors of childhood cancer (Tutelman & Heathcote, 2020), very little is known about the experience of FCR in child survivors and their parents. Study 3 (Chapter 4) presents new measures of FCR in survivors of childhood cancer and their parents. While more research is needed to further validate the scales and determine appropriate clinical cut-off scores, findings in Studies 3 and 4 (Chapters 4 and 5) suggest that child survivors do in fact experience FCR and a significant minority experience it at high levels. Parents of childhood cancer survivors reported, on average, clinically-elevated levels of FCR, flagging this group as high priority for clinical attention. Screening for FCR in survivors of childhood cancer and their parents may be warranted. While numerous FCR interventions have been developed for adult cancer survivors (Tauber et al., 2019) and interventions are undergoing testing for caregivers (Lamarche et al., 2021), no targeted interventions exist for children or parents. Findings from Study 4 (Chapter 5) highlight pain catastrophizing as a key cognitive process associated with FCR in childhood cancer survivors and their parents. Indeed, interventions for pediatric chronic pain often target pain catastrophizing and have found it to be responsive to treatment (Coakley et al., 2018; Kashikar-Zuck et al., 2013;

Levy et al., 2017; Lomholt et al., 2015). This dissertation points to pain catastrophizing as a novel and salient target to address in interventions developed FCR in survivors of childhood cancer and their parents.

6.4. Key Strengths and Limitations

The current dissertation has several key strengths. First, the use of multiple methods offered a comprehensive investigation of pain after childhood cancer from multiple perspectives. The studies that comprise the dissertation employed several rigorous methods, including qualitative (IPA; Study 1, Chapter 2), experimental pain (QST; Study 2, Chapter 3), and questionnaire-based (Studies 3 and 4, Chapters 4-5) approaches. Pain is defined as a multidimensional experience that is inherently subjective and personal in nature (Raja et al., 2020). The use of multiple methods in this dissertation allowed for the examination of the various dimensions of pain, ranging from individuals' narratives of their lived experience (Study 1, Chapter 2), to the functioning of the pain and sensory system (Study 2, Chapter 3), and survivors' self-report using validated questionnaire items (Study 4, Chapter 5). Each method employed in this thesis has its own inherent strengths and limits (addressed specifically in each respective chapter). For instance, while IPA does not seek to produce generalizable findings, the results do reflect the experiences of a rather small number of individuals. Similarly, while QST employs standardized methods with calibrated stimuli, results may be vulnerable to contextual factors. Further, while the questionnaire-based methods allowed for the valid and reliable assessment of various constructs, the studies captured individuals' perspectives at one moment in time and thus cannot speak to the directionality of the relationships identified. That said, taken together, the data presented in this multimethod dissertation collectively

offer a richer and more complete picture of pain in childhood cancer survivorship than each of the components would have on their own. Second, the patient-oriented nature of this thesis was a significant strength of this dissertation. Patient partners were engaged across all stages of the dissertation and made significant contributions to the design, recruitment, analysis, and dissemination of the studies, ultimately resulting in research that is more relevant and clinically useful (as described above). Third, the inclusion of both child and parent reports in Studies 1, 3, and 4 (Chapters 2, 4, and 5) offered an important dyadic perspective. Children do not exist in isolation and the family context is highlighted as an important factor to consider in their experience of pain (Palermo & Chambers, 2005). Including both children and parents as participants allowed for consideration of both children's and parents' experiences and the relationship between them.

This dissertation overall also has limitations which should be acknowledged. First, the quantitative studies in this dissertation (Studies 2-4, Chapters 3-5) were limited by their relatively small sample sizes. This was due in part to the COVID-19 pandemic which resulted in the early termination of recruitment in March 2020. The target sample size for the QST study (Chapter 3) was 60 survivors of childhood cancer. Given that the study was only a few participants away from reaching the target, the impact was likely negligible. That said, the recruitment pool of childhood cancer survivors in Maritime Canada is relatively small, and participants were required to travel (some interprovincially) to attend the in-person QST session. Nevertheless, the modest sample size may have precluded the identification of smaller effects, particularly those that are dyadic in nature (i.e., the relationship between parent and child variables). Second, while

the studies in this dissertation purposefully included participants with diverse demographic (e.g., age, sex) and clinical (e.g., cancer type, time off treatment) characteristics, the racial and sociodemographic diversity of those included was limited and certain cancer types (e.g., CNS tumours) were underrepresented, as were fathers. Future research should employ targeted efforts (e.g., in-clinic recruitment, partnerships with relevant patient advocacy groups) to promote diversity in this area. Further, some families invited to participate in the dissertation studies did not respond or declined to participate. It is possible that those who participated had specific interests in the study topics or were ones willing to revisit their experience of cancer. Thus, it is unclear how well those who did participate represent the broader survivor community. It is important to consider the impact of these factors on the generalizability of the findings. Additionally, childhood cancers are quite heterogeneous with regards to their pathophysiology, treatments, and prognosis (Erdmann et al., 2021). The 'lumping together' of children with various forms of cancer may have overlooked certain nuances relevant to pain and FCR that may be specific to certain cancer types. Third, the cross-sectional and correlational nature of the data in this dissertation, including the lack of a pre-diagnosis time point, limits conclusions regarding the directionality and temporality of the findings. Relatedly, is important to note that the cross-section of data was not at a uniform time point from the end of treatment for all participants, which is a factor that could impact their experiences of pain both physically and psychologically.

6.5. Future Research Directions

In recent years, the fields of pain and psychosocial oncology have become increasingly interested in understanding the experience of pain after childhood cancer.

Findings in the current dissertation add to the growing literature and provide a solid foundation of empirical data on which future research can build. Recommendations for future research specific to the findings of each study are described in the relevant chapters. Reflections on general directions for future research are outlined below.

The experience of pain after childhood cancer is complex. As described in the Introduction to the dissertation, there are many variables that likely collectively influence the experience of pain and sensation following treatment for childhood cancer. These range from exposure to neurotoxic drugs and procedures (Burgoyne et al., 2012; Kandula et al., 2018; Kroczka et al., 2021; Weisman et al., 1998), to the effects of the underlying disease process (De Martino et al., 2019) and a survivor's psychosocial functioning (Lumley et al., 2011; Weissman-Fogel et al., 2008). It is unlikely that one of these variables alone could fully account for a survivor's experience of pain after cancer. Many of these potential factors could significantly contribute to the pain in survivors of childhood cancer both singly and in clusters. Based on what is known about the susceptibility of the developing nervous system to insult (Andrews et al., 2002; Walker et al., 2009), there are also likely interactions between variables such as neurotoxic drug exposure and demographic factors such as the age of the child at exposure. Recent research has also focused on genetic mutations that may make some survivors more susceptible to neurological sequalae, such as neuropathy and pain (Egbelakin et al., 2011). A large sample would be required to test the contributions and interactions of these variables. A study of such magnitude is made complex by the relative paucity of children who are treated for cancer at any one centre, with only a fraction of those eligible and able to attend in person components (e.g., a QST protocol). Furthermore,

most studies to date examining pain in survivors of childhood cancer are cross-sectional in nature. To comprehensively understand the contribution of different variables to the development and maintenance of pain in survivors of childhood cancer, evaluation of pain and sensory processing, by self-report and/or sensory testing, should be conducted at carefully planned intervals and include timepoints before treatment, throughout treatment and into survivorship. Multisite studies with larger numbers of participants that proportionally represent the various forms of childhood cancer, are diverse in demographic characteristics, and that include longitudinal data are needed to understand pain in this complex population. These data will be crucial for developing mechanism-based pain prevention and intervention measures in this population.

6.6. Concluding Remarks

The current dissertation advances the literature on pain in survivors of childhood cancer using several rigorous methods. First, an in-depth qualitative study (Chapter 2) found that pain is a changed experience for survivors of childhood cancer and their parents and may be interpreted as a threat of recurrence. Using a standardized QST protocol, the second study (Chapter 3) revealed pervasive differences in survivors' pain and sensory processing compared to reference data that is present years after treatment completion. Demographic, clinical, and psychosocial risk factors for differences in sensory processing were identified. In Study 3 (Chapter 4), psychometrically strong measures of FCR were developed for childhood cancer survivors and their parents. In the final study (Chapter 5), the quantitative relationship between anxiety symptoms, pain intensity, pain catastrophizing and FCR were established in survivors of childhood cancer and their parents. This study highlighted the central contribution of the cognitive

components of pain to children's and parents' experiences of FCR. Taken together, the results of this dissertation contribute to the understanding of pain after childhood cancer and its relationship with FCR. Findings point to potential targets for intervention for this complex population.

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CC: Christine Chambers, Pain J
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